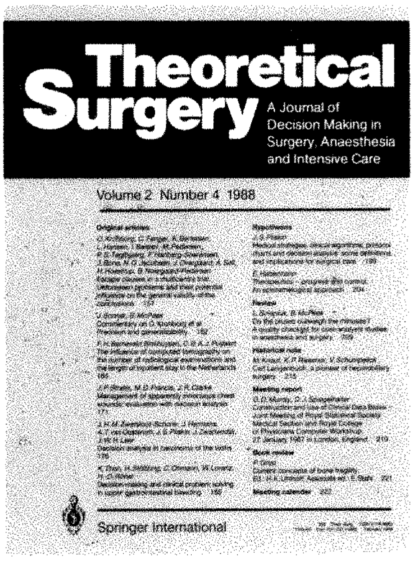
he British
ournal of Surgery

ne 75, Number 7, July 1988

Vol-75
No.-7-10
1988

16



Theoretical Surgery

A Journal of
Decision Making in
Surgery, Anaesthesia
and Intensive Care

ISSN 0179-8669 Title No. 385

THEORETICAL SURGERY publishes contributions on all non-operative aspects of the care of the surgical patient including anaesthesia and intensive care. Included is methodology and application of clinical decision making in surgery, progress and problems in clinical trials, basic research in surgical patients, cost benefit analysis and audit, risk analysis, controversies, philosophy, ethics and history. Contributions are in the form of original papers, reviews hypotheses, editorials, short communications and letters. Books are also reviewed.

Editors: W. Lorenz, Institute of Theoretical Surgery, Philipps-University of Marburg, Baldinger Str., D-3550 Marburg/FRG
J. H. Baron, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 OHS, England

Editorial board: H. G. Beger, Ulm; S. Bengmark, Lund; A. Doenicke, München; F. T. de Dombal, Leeds; M. Fisher, St. Leonards; Ch. Herfarth, Heidelberg; M. Hobsley, London; R. Knill-Jones, Glasgow; O. Kronborg, Odense; F. Largiadèr, Zürich; I. McColl, London; M. F. McKneally, Albany; B. McPeek, Boston; K. Meßmer, Heidelberg; C. Ohmann, Düsseldorf; J. S. Pliskin, Beer Sheva; V. Schumpelick, Aachen; D. J. Spiegelhalter, Cambridge; H. Troidl, Köln; J. Watkins, Sheffield

Subscription Information:
1988. Volume 3 (4 issues): DM 168,–, plus carriage charges. Please send your order or request to your bookseller or to: Springer-Verlag, Heidelberger Platz 3, D-1000 Berlin 33, FRG

North America
US $ 103.50 including carriage charges. Subscriptions are entered with prepayment only. Please send your order or request to: Springer-Verlag, New York Inc., Service Center Secaucus, 44 Hartz Way, Secaucus, NJ 07094, USA

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Heidelberger Platz 3, D-1000 Berlin 33
175 Fifth Ave., New York, NY 10010, USA
28, Lurke Street, Bedford MK40 3HU, England
26, rue des Carmes, F-75005 Paris
37-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan
Room 1603, Citicorp Centre, 18 Whitfield Road, Causeway Bay, Hong Kong

A selection of articles from Volume 2, 1987/88

Original articles

O. Kronborg, C. Fenger, K. Bertelsen, L. Hansen, I. Balslev, M. Pedersen, P. S. Teglbjaerg, F. Hanberg-Soerensen, J. Bone, N. O. Jacobsen, J. Overgaard, A. Sell, H. Hoestrup, B. Noergaard-Pedersen
Escape clauses in a multicentre trial. Unforeseen problems and their potential influence on the general validity of the conclusions

J. P. Stratis, M. D. Francis, J. R. Clarke
Management of apparently innocuous chest wounds: evaluation with decision analysis

P. Carpentier, C. Sulman, B. Lemaire, L. Eeckhoudt, P. Gosselin, J. L. Cazin
Decision tree and sensitivity analysis as an aid for the management of the solitary thyroid nodule

J. S. Pliskin, D. Pilpel, S. Ilani
Economic considerations and size determination of a surgical day-care unit

M. Hobsely, P. F. Whitfield
The likelihood of a disease in relation to the magnitude of a risk factor. The example of duodenal ulcer

E. Neugebauer, W. Lorenz, D. Maroske, W. Barthlen, M. Ennis
The role of mediators in septic/endotoxic shock. A meta-analysis evaluating the current status of histamine

Hypotheses

S. P. Allwork
Anatomical versus embryological nomenclature in cardiac malformations exemplified by interatrial communications

E. Habermann
Therapeutics – progress and control. An epistemological approach

Reviews

J. Eldor, D. Z. N. Frankel, J. T. Davidson
Perioperative myocardial reinfarction

L. Soloniuk, B. McPeek
Do the pluses outweigh the minuses? A quality checklist for cost-analysis studies in anesthesia and surgery

Historical notes

H. Taylor
Recollections of an early surgical gastroscopist

U. Klinge, M. Weeg, V. Schumpelick
Ludwig Rydygier – pioneer of gastric resection for ulcers

Meeting report

J. Kusche, H. Troidl
Microcomputers in Surgery. 6th Meeting of the Permanent Working Party on Clinical Studies (CAS)of the German Surgical Society, 8-9 November 1985 in Cologne, Federal Republic of Germany

sb. 20.261/4/1

Springer

P 25,330
COH-H06200-16-P25330

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Volume 75 Number 7 July 1988

16

LEADING ARTICLES

Surgery for constipation 625
M. R. B. Keighley

Pancreatic transplantation 627
P. J. Morris

REVIEWS

Variations in surgical practice: welcome diversity or disturbing differences 630
B. Jennett

Traumatic retroperitoneal venous haemorrhage 632
S. R. G. Smith

Management of major colonic haemorrhage 637
A. R. Berry, W. B. Campbell and M. G. W. Kettlewell

Growth rate of hepatic metastases in colorectal carcinoma 641
I. G. Finlay, D. Meek, F. Brunton and C. S. McArdle

Operative mortality rate and surgery for colorectal cancer 645
S. C. W. Brown, S. Walsh and P. A. Sykes

Penetrating arrow injuries (case report) 647
R. Visvanathan

Clinicopathological assessment and staging of colorectal cancer 649
N. S. Williams, J. R. Jass and J. D. Hardcastle

Natural history and treatment of anorectal strictures complicating Crohn's disease 653
L. Linares, L. F. Moreira, H. Andrews, R. N. Allan, J. Alexander-Williams and M. R. B. Keighley

Role of constipation and anal hypertonia in the pathogenesis of haemorrhoids 656
C. P. Gibbons, J. J. Bannister and N. W. Read

Lateral division of the puborectalis muscle in the management of severe constipation 661
M. A. Kamm, P. R. Hawley and J. E. Lennard-Jones

REVIEW

The task of a statistical referee 664
G. D. Murray

Intravenous digital subtraction angiography and Duplex scanning in the detection of late human umbilical vein degeneration 668
A. Nevelsteen, G. Smet, G. Wilms, G. Marchal and R. Suy

Effects of autologous mesothelial cell seeding on prostacyclin production within Dacron® arterial prostheses 671
H. A. Bull, R. M. Pittilo, J. Drury, J. G. Pollock, J. M. F. Clarke, N. Woolf, A. Marston and S. J. Machin

Hydroxyethyl starch: an alternative to plasma for postoperative volume expansion after cardiac surgery 675
C. M. Munsch, E. MacIntyre, S. J. Machin, I. J. Mackie and T. Treasure

Clinical observations on the wound healing properties of honey 679
S. E. E. Efem

Effect of surgery on neutrophil functions, superoxide and leukotriene production 682
J. Utoh, T. Yamamoto, T. Utsunomiya, T. Kambara, H. Goto and Y. Miyauchi

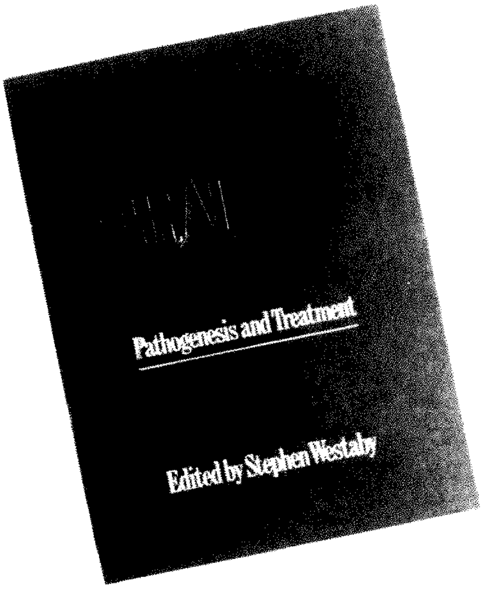
The medical response to injury and violence —

TRAUMA

Pathogenesis and Treatment

Edited by
Stephen Westaby BSc, MS, FRCS

Foreword by Professor Miles Irving



A comprehensive survey of trauma and its medical and surgical management, this impressive book, illustrated in full colour, contains contributions from the world's leading trauma specialists. The book reviews critically the worldwide pandemic of trauma, its causes and its early management. Chapters are devoted to the mechanisms of injury and the physiological responses to trauma. Triage, retrieval and trauma scoring are re-examined, and surgical intervention is described on a regional basis.

A topical work of considerable authority, for all clinicians dealing with the victims of trauma.

ISBN: 0 433 35502 6/400pp £65.00
Full colour illustrations throughout

Publication of this work has been made possible with the assistance of a grant towards origination costs from the family of Johnson and Johnson Medical Companies in the UK.

Heinemann Medical Books
Halley Court
Jordan Hill
OXFORD OX2 8EJ

NEW FROM BUTTERWORTHS

Positioning the Surgical Patient

J. M. Anderton, FFARCS Consultant Anaesthetist, Manchester Royal Infirmary **R. I. Keen,** FFARCS Consultant Anaesthetist, Manchester Royal Infirmary **R. Neave,** FMAA Medical Artist, University of Manchester

★ Explains clearly the 'how' and 'why' of patient positioning. ★ Superb illustrations demonstrate all important positioning techniques. ★ Indispensable to anyone working in the operating theatre.

The correct positioning of the surgical patient is of vital importance to a successful outcome. Each type of operation demands that the patient be placed in a particular way, but for each position there are associated problems and risks. This is the first short textbook to explain the 'how' and 'why' of patient positioning, and it does so in a clear and comprehensive manner.

The authors use a carefully integrated mixture of text and line illustrations to describe the purpose of the main surgical positions. For each, they then cover in detail the associated anatomical hazards; the specific techniques required to achieve the correct position – illustrated with action sequences drawn from actual operative situations; and conclude with variants of the basic positions. A final chapter on respiratory and circulatory aspects highlights the physiological implications for the patient of the different positions.

Although precise details of practice vary from hospital to hospital, the authors concentrate on the principles rather than the minutiae. The result is a textbook which should have broad appeal to anyone with operative surgical responsibilities. This includes surgical and anaesthetic staff, who have the primary task of selection and general implementation of patient position, as well as nurses and operating department assistants who play an indispensable role in its detailed execution.

CONTENTS The supine position • The lithotomy position • The lateral position • The prone position • The sitting position • The transfer of patients and recovery room practice • Specialized positions • Physiological effects of posture in the anaesthetised patient • Index *March 1988 128 pages 246 x 189 mm Softcover 156 line illustrations 0 407 012206 £12.95*

For details of other Butterworth Scientific titles, please contact the appropriate office.
Orders should be sent to the appropriate office listed below.
The UK headquarters serves all UK and overseas markets except where there is a local Butterworths office.

United Kingdom
Butterworths, Borough Green
Sevenoaks, Kent TN15 8PH
England

Customers in Asia may order through:
Butterworth & Co (Asia) Pte Ltd
30 Robinson Road, Unit 12-01 Tuan Sing Towers
Singapore 0104, Republic of Singapore

USA & Canada
Butterworth Publishers
80 Montvale Avenue
Stoneham, MA 02180, USA

Australia & Papua New Guinea
Butterworths Pty Ltd, PO Box 345
North Ryde, New South Wales 2113
Australia

New Zealand
Butterworths of New Zealand Ltd
33-35 Cumberland Place
Wellington 1, New Zealand

Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery 686
M. R. Lassen, L. C. Borris, H. M. Christiansen, F. Møller-Larsen, V. E. Knudsen, P. Boris, A.-M. Nehen, A. de Carvalho, A.-G. Jurik, B. W. Nielsen and U. Lucht

An operation for incisional hernia (surgical workshop) 689
F. E. Weale

Oxygen consumption following trauma: a reappraisal in severely injured patients requiring mechanical ventilation 690
J. D. Edwards, A. D. Redmond, P. Nightingale and R. G. Wilkins

Enterostomy as an adjunct to treatment of intra-abdominal sepsis 693
W. L. E. M. Hesp, E. J. C. Lubbers, H. H. M. de Boer and T. Hendriks

Screening for breast cancer: some clinical aspects 697
A. D. Stockdale, P. Last, A. K. Tucker and J. Meirion Thomas

Microdochectomy for single-duct discharge from the nipple 700
A. P. Locker, M. H. Galea, I. O. Ellis, H. W. Holliday, C. W. Elston and R. W. Blamey

Breast cyst type does not predict the natural history of cyst disease or breast cancer risk 702
S. R. Ebbs and T. Bates

Artefactual body wall ecchymosis in acute pancreatitis (case report) 704
C. Wilson

Effect of vertical banded gastroplasty on the natural history of gastritis in patients with morbid obesity: a follow-up study 705
J.-F. Flejou, E. R. T. C. Owen, A. C. Smith and A. B. Price

Treatment of stomach cancer, a national experience 708
B. Valen, A. Viste, T. Haugstvedt, G. E. Eide, O. Søreide and Members of the Norwegian Stomach Cancer Trial

Role of adhesive wraps in the pathogenesis of complicated amoebic colitis 713
F. M. Luvuno

Cure of a bleeding duodenal varix by sclerotherapy (case report) 717
Ph. Gertsch and L. H. Blumgart

Treatment of pancreatic fistula with the somatostatin analogue SMS 201-995 (case report) 718
B. Ahrén, K.-G. Tranberg and S. Bengmark

Limited conservative pancreatectomy for benign tumours: a new technical approach (surgical workshop) 719
P.-L. Fagniez, M. Kracht and N. Rotman

Determining safe margin of resection in low anterior resection for rectal cancer (short note) 720
W. O. Kirwan, J. Drumm, J. M. Hogan and C. Keohane

True aneurysms of the pancreaticoduodenal artery: a rare cause of retroperitoneal bleeding and delayed diagnosis (short note) 721
D. J. Small, P. W. J. Houghton and N. J. McC. Mortensen

Bowel movement and diet in patients with stomas (short note) 722
F. Giunchi, G. Cacciaguerra, M. L. Borlotti, A. Pasini and G. Giulianini

CORRESPONDENCE 723

BOOK REVIEWS 726

NOTICES AND ANNOUNCEMENTS 728

Cover picture

Lord Moynihan Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA).

Editorial Committee

Chairman
C. W. Jamieson, *London*

Vice-Chairmen
J. L. Dawson, *London*
H. B. Devlin, *Stockton-on-Tees*

Editors
R. C. G Russell, *London*
D C Carter, *Glasgow*

Associate Editor
A. E Young, *London*

Statistical Consultant
G. D Murray, *Glasgow*

T. Bates, *Ashford*
K. G Burnand, *London*
(*Surgical Research Society*)
J D. Hardcastle, *Nottingham*
A. G. Johnson, *Sheffield*
M. R B. Keighley, *Birmingham*
J A P. Marston, *London*
A. N. Nicolaides, *London*
(*Royal Colleges of Surgeons*)
I Taylor, *Southampton*
(*Association of Surgeons*)
N. S Williams, *London*
R. C. N Williamson, *London*

Editorial Board

A. P. R. Aluwihare, *Sri Lanka*
E Q. Archampong, *Ghana*
J. H Baron, *London*
J. Bergan, *USA*
K. Bielecki, *Poland*
H. Bismuth, *France*
P C Bornman, *South Africa*
D Bouchier-Hayes, *Dublin*
W H. Brummelkamp, *The Netherlands*
R. Carpenter, *Jamaica*
A Cuschieri, *Dundee*
B Eklof, *Kuwait*
E A. Elebute, *Nigeria*
J. R Farndon, *Newcastle upon Tyne*
J M. Fitzpatrick, *Dublin*
Sir Patrick Forrest, *Edinburgh*
W D George, *Glasgow*
G. R. Giles, *Leeds*
I E Gillespie, *Manchester*
B. C Golematis, *Greece*
J. F. Grenier, *France*
F. Harder, *Switzerland*
M A. Hassan, *Sudan*
R J Heald, *Basingstoke*
G. L. Hill, *New Zealand*
T Hirayama, *Japan*
E. R. Howard, *London*
L Hulten, *Sweden*
M H Irving, *Manchester*
G. G. Jamieson, *Australia*
J Jeekel, *The Netherlands*
H.-E Jensen, *Denmark*
K. A. Kelly, *USA*
J A. Mannick, *USA*
T G Parks, *Belfast*
A Pausawasdi, *Thailand*
C Pera, *Spain*
H C Polk, *USA*
A. T. Raftery, *Sheffield*
N. Rangabashyam, *India*
J H C Ranson, *USA*
C. V. Ruckley, *Edinburgh*
S Shionoya, *Japan*
J C. Smith, *Oxford*
K. Somasundaram, *Malaysia*
T. E. Starzl, *USA*
H. Stone, *USA*
D E Strandness Jr, *USA*
G Teasdale, *Glasgow*
M. Trede, *West Germany*
D. E. F. Tweedle, *Manchester*
A Watson, *Lancaster*
R. W. Webb, *USA*
D J. T Webster, *Cardiff*
F. R Wilkes, *Armed Forces*
D Wilmore, *USA*
J Wong, *Hong Kong*
R. F. M Wood, *London*

Instructions to Authors

Original articles and other editorial matter including books for review should be sent to: The Editor, *The British Journal of Surgery*, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK. Acceptance of original material is on the understanding that contributions are to this Journal only and that articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title should indicate if the paper is based on a previous communication to a society or other meeting.

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1979; **1**: 502–72 or *Lancet* 1979; **1**: 428–31 or to obtain the leaflet *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, from the Editor, *British Medical Journal*, BMA House, Tavistock Sq., London WC1H 9JR (enclose 50p).

The recommendations below are a summary of *Uniform Requirements* and are those which contributors must observe to ensure acceptance of their manuscripts at the Journal Office.

Submit three good quality plain paper photocopies of all written and tabular material and retain the original. A covering letter must be signed by all authors and must state: if an abstract of the work has been published; and whether the manuscript and/or illustrations are to be returned. Otherwise rejected material will be held for 3 months and then shredded. The manuscript should be typed double spaced with 3 cm margins on ISO A4 (212 × 297 mm) paper or near equivalent and in the following sequence, beginning each section on a new page: title page with authors (give initials only for men; one Christian name for women), their highest academic qualification, addresses and the author or individual to whom correspondence relating to the paper should be sent; abstract and keywords (3–10 words or phrases using terms from *Index Medicus* whenever possible); text (usually, but not exclusively: introduction, methods, results, discussion); acknowledgements; references; tables; and legends for illustrations. The abstract must be complete in itself, outlining the aim, results and conclusions of the paper. Tables should be typed each on a separate sheet and *must* have an Arabic identifying number and a short descriptive heading. Pages *must* be numbered and a 'ragged' right margin is preferred. Submit all illustrations in triplicate and package securely. Photographs should be good quality, unmounted, glossy prints (not X-ray negatives or slides). Line drawings should be professionally drawn and photographed. A leaflet giving details of preparation of artwork is available from the Editorial Office (enclose s.a.e.) and must be consulted if extra costs are not to be incurred by authors. Unsatisfactory artwork will be returned for redrafting. A comprehensive guide to drafting is given by *Charts and Graphs*, ed. Doig Simmonds, MTP Lancaster, 1980. Colour prints should be accompanied by the original transparencies or negatives: a contribution towards the cost of colour reproduction is nearly always necessary All illustrations should have a label pasted on the back indicating the name of the author(s), the figure number and the orientation and, for micrographs, original magnification. Do not write in pencil or ink on the back of photographs.

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached.

Numbers, SI units and abbreviations. The decimal point, not a comma, is used: 5·69 not 5,69. A space rather than a comma follows thousands and multiples thereof: 10 000 not 10,000. It is journal policy to use SI units except for measurement of blood pressure (mmHg). Energy may be expressed as either kilocalories or megajoules though the latter is preferred as the primary figure followed by kilocalories in parentheses: 5·69 MJ (1360 kcal). Abbreviations for both SI units and statistical terms are those in Baron D. N. (comp): *Units, Symbols and Abbreviations· a Guide for Biological and Medical Editors and Authors*, 3rd ed. London, Royal Society of Medicine, 1977, *Br Med J* 1978; **1**: 1334–6 and *The SI for the Health Professions*, World Health Organization, Geneva, 1977. Other useful works are: Council of Biological Editors: *CBE Style Manual*, 3rd ed. Washington, American Institute of Biological Sciences, 1972; and O'Connor M. and Woodford P.· *Writing Scientific Papers in English, an ELSE-Ciba Foundation Guide for Authors*. London: Pitman, 1978.

References. In the text, references should be numbered consecutively by superscript· ^{1,2} or $^{1-3}$. References cited only in tables and figures should be numbered in sequence according to the first mention of the table or figure in the text. Journals should be cited using the form of title adopted by *Index Medicus*; if the journal is not listed by *Index* give the full title. Up to six authors can be listed, if the number exceeds six quote the first three followed by *et al.*

The sequence for a standard journal article is: author(s), title, journal, year, volume, first and last page numbers. The layout and punctuation which should be used for *Br J Surg* are:

De Cossart Linda, Marcuson RW. Vascular plasminogen activator and deep vein thrombosis. *Br J Surg* 1983; **70**: 369–70.

The sequence for a book is: author(s), editor(s) or compiler(s); title; edition number; place of publication; publisher's name; year of publication, first and last pages of reference (if relevant). The layout and punctuation are:

Ellis H, Calne RT. *Lecture Notes on General Surgery* 5th ed. Oxford: Blackwell, 1977.

The British Journal of Surgery is published monthly by Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK. Telephone: 0483 300966. Telegrams and Telex 859556 SCITEC G. Registered office: Butterworth Scientific Limited, 88 Kingsway, London WC2 6AB, UK.

Managing Editor: Sarah Graham-Campbell
Sub-Editor June Greig-Smith
Production: Julia Sentance
Advertisement Sales Representative: Mark Butler

UK and Overseas subscription orders should be sent to: Westbury Subscription Services, P O. Box 101, Sevenoaks, Kent TN15 8PL, UK. Telephone: 0732-885833. Telex: 95678. Facsimile: 0732-884079 Cable: Westbury, Sevenoaks, Kent. **North American orders** should be sent to· Journals Fulfilment Department, Butterworths, 80 Montvale Avenue, Stoneham, MA 02180, USA Telex· 880052 Telephone: (617) 438 8464

The annual subscription to **The British Journal of Surgery** (12 issues) for UK readers is £59.00, single copies £6.00 and personal subscription £47.00 Overseas rates are annual subscription £70.00, single copies £7 00 and personal subscription £47.00. These prices include delivery by sea mail, airmail rates are available on request. For North America rates are: annual subscription £70 00, single copies £7.00, personal subscription £47.00 Copies of this journal sent to subscribers in Australasia, Bangladesh, Canada, India, Pakistan, Sri Lanka and USA are air-speeded for quicker delivery at no extra cost

Back issues prior to the current volume are available from Wm Dawson & Sons Ltd, Cannon House, Folkestone, Kent, England CT19 5EE. Telephone: 0303 57421

US mailing agents. Mercury Airfreight International Ltd Inc Second class postage paid at Rahway, NJ, USA Postmaster. send address corrections to *The British Journal of Surgery*, c/o Mercury Airfreight International Ltd Inc., 10B Englehard Avenue, Avenel, NJ 07001, USA

A microfilm version of **The British Journal of Surgery** is available Please contact University Micro Films Inc , 300 N Zeed Road, Ann Arbor, Michigan, MI 48106, USA

Copyright: Readers who require copies (minimum quantity 100) of papers published in this journal may either purchase reprints or obtain permission to copy from the publisher For readers in the USA, permission to copy is given on the condition that the copier pays the stated per copy fee through the Copyright Clearance Center Inc , 27 Congress Street, Salem, MA 01970, USA (617) 744-3350 for copying beyond that permitted by Sections 107 and 108 of the US Copyright Law Fees appear in the code that appears at the foot of the first page of each paper. This journal is listed in 'Current Contents'

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the Publisher.

ISSN 0007-1323

Filmset by Mid-County Press, London SW15 Printed by The Friary Press Ltd. Dorchester and London.

Br. J. Surg. 1988, Vol. 75, July, 625–626

Surgery for constipation

Surgeons should not become embroiled in treating constipation! This sentiment is probably widely held by readers of *The British Journal of Surgery*. Can surgeons really justify taking out a normal colon? For most, this philosophy became taboo with the departure of Arbuthnot Lane[1] from the surgical scene.

Constipation has a wide variety of causes, can present with serious complications, and there is a large psychosomatic undercurrent despite physiological abnormality. Increasing clinical application of sophisticated physiological monitoring facilities and hormone assay has unquestionably increased our understanding of the mechanisms responsible for impaired colonic and rectal motility. Since surgeons have been at the forefront of many of these physiological advances, it is hardly surprising that they have also turned their hand to exploring the role of surgery in the therapy of chronic intractable constipation.

As in all branches of medicine, the clinician must exclude congenital and acquired disorders which could be responsible for constipation. Drugs such as opiates, aluminium or calcium containing antacids, anticholinergic drugs, antihistamines and a host of antidepressants may constipate. Chronic laxative abuse probably results in damage to the intrinsic autonomic nerve plexus of the colon[2]. Endocrine disorders which may constipate include myxoedema, panhypopituitary syndromes, hyperparathyroidism, phaeochromocytoma and glucagonomas, to mention but a few. Patients frequently date the onset of constipation to an event which disturbs normal ovarian function such as the menarche, the menstrual cycle, use of the contraceptive pill, pregnancy or hysterectomy. Constipation following simple hysterectomy may be hormonal or may result from damage to the pelvic autonomic plexus. Certainly, irregular periods, galactorrhoea and infertility are more common in constipated patients than controls[3]. Specific hormonal abnormalities include raised prolactin levels, low urinary oestrogen excretion and low plasma oestrogen concentrations. Other hormones which may be implicated include gastrin, pancreatic polypeptide, motilin, glucagon and vasoactive intestinal peptides. Few patients with peripheral neurological disorders develop constipation but high cord compression is commonly bedevilled by faecal impaction. Previous cerebrovascular accident, Parkinson's disease and some demyelinating disorders may result also in intractable constipation.

Since constipation is only a symptom, readers will not need reminding that primary organic pathology in the large bowel should also be excluded, notably benign or malignant colorectal strictures, volvulus, rectal prolapse (especially in the young), solitary ulcer, congenital or acquired aganglionosis and megacolon. Standard radiological assessment may be unreliable in identifying megarectum. Furthermore, absence of the recto-anal inhibitory reflex does not necessarily imply Hirschsprung's disease, since the reflex may be absent in incontinent patients and after previous operation. The reflex may be preserved in short segment aganglionosis[4]. Some form of physiological assessment unquestionably helps to identify a primary functional abnormality and allows rational therapy to be planned for patients with intractable symptoms. Most coloproctology units are now equipped with manometric, electromyographic, isotopic and video proctographic facilities for measurement of colonic transit, rectal emptying, pelvic floor function, sphincter reflexes and anorectal sensation.

Perhaps a word of caution is needed, since demonstration of a physiological abnormality does not necessarily imply that surgical correction is advisable. A most important aspect of the history is to exclude severe psychiatric disorder, personality disturbance or the use of psychotropic drugs. Constipated patients have significantly higher anxiety and depression scores compared with a matched control population[5]. More importantly, high anxiety and depression scores predict a poor outcome after surgical treatment.

Despite this, most coloproctologists now accept that subtotal colectomy and ileorectal anastomosis provides acceptable relief of symptoms for megacolon. Rectal excision using the Soave or Duhamel reconstruction sometimes gives reasonable functional results for megarectum[6] but, if the colon is dilated as well, restorative proctocolectomy and pouch–anal anastomosis has prevented construction of a

0007–1323/88/070625–02$3 00

permanent stoma in some patients (M. R. B. Keighley *et al.*, unpublished results). Subtotal colectomy and either ileorectal or caecorectal anastomosis is less reliable for slow transit constipation since some patients suffer from intractable diarrhoea, a few still cannot defaecate, and the majority still have abdominal pain and distension[7].

If colectomy is controversial, operation for pelvic floor disorders is regarded by most coloproctologists as speculative! The paper by Kamm and his colleagues from St. Mark's Hospital in this issue of the Journal (pp. 661–663) provides an honest assessment of the place of partial puborectalis division for outlet obstruction. Preoperative assessment revealed impaired rectal evacuation and electromyographic evidence of increased activity in the puborectalis on attempted defaecation. Despite this, only 4 of 18 patients were improved by unilateral or bilateral division of the lateral fibres of the puborectalis. This is similar to their earlier disappointing experience with posterior puborectalis division[8]. An alternative option is anorectal myectomy. This procedure was first used in paediatric practice to exclude Hirschsprung's disease but has recently been applied as a diagnostic procedure in adults with outlet obstruction. The operation involves excising a strip of internal anal sphincter and rectal circular muscle over a length of 10–12 cm. Approximately 15–20 per cent of patients are found to have an aganglionic segment and short term symptomatic improvement is reported in 60–70 per cent of patients. The operation results in improved rectal emptying and reduced anal pressures during defaecation, but the electromyographic abnormality in the pelvic floor usually persists[10]. Only time will tell whether this and other operations in constipated patients with objective evidence of a pelvic floor abnormality will fall into disrepute. The track record of most surgical procedures for disorders having a physiological abnormality but with exaggerated psychiatric overtones is a dismal one of failed surgical endeavour. Caution should probably be exercised until long term benefit can be substantiated from more than one centre.

M. R. B. Keighley

General Hospital
Birmingham B4 6NH
UK

1. Lane WA. Chronic intestinal stasis. *Br Med J* 1909; 1. 1408–11.
2. Smith B, Grace RA, Todd IP. Organic constipation in adults. *Br J Surg* 1977; **64**: 313–14.
3. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: idiopathic slow transit constipation. *Gut* 1986; **27**. 41–8.
4. Fisher SE, Keighley MRB, Breckon K, Smart V, Andrews H. Do patients with disordered defaecation have a primary personality disorder? *Gut* 1987; **28**: A1373.
5. Shouler P, Keighley MRB. Changes in colorectal function in severe idiopathic chronic constipation. *Gastroenterology* 1986; **90**: 414–20.
6. Lane RHS, Todd IP. Idiopathic megacolon: a review of 42 cases. *Br J Surg* 1977; **64**: 303–10.
7. Kamm MA, Hawley PR, Lennard-Jones JE Is colectomy for severe idiopathic constipation a success? *Gut* 1987; **28**: A1343.
8. Barnes PRH, Hawley PR, Preston DM, Lennard-Jones JE. Experience of posterior division of the puborectalis muscle in the management of chronic constipation. *Br J Surg* 1985; **72**. 475–7.
9. Yoshioka K, Keighley MRB Anorectal myectomy for outlet obstruction. *Br J Surg* 1987; **74**: 373–6.
10. Yoshioka K, Keighley MRB. Randomized trial comparing anorectal myectomy and controlled anal dilatation for outlet obstruction. *Br J Surg* 1987; **74**: 1125–9.

Br. J. Surg. 1988, Vol. 75, July, 627–629

Pancreatic transplantation

Insulin-dependent diabetes is one of the most ravaging diseases of the western world, mainly because of its macro- and micro-angiopathic complications. For example: diabetes is the major cause of blindness under the age of 60 years; it is the fifth major cause of end-stage renal failure; some 20 per cent of amputations are performed in diabetics; cardiovascular disease is a major cause of death in diabetics; and all of these problems lead to a life expectancy which is 10–15 years less than that of the non-diabetic population. It has always been received wisdom that good control of blood glucose levels over a 24 h period would reduce the incidence and severity of these micro-angiopathic complications. In recent years there has been considerable evidence that this is indeed so, and it is hoped that the results of two large controlled trials in the USA and the UK, in type I (insulin dependent) and type II (mature onset) diabetes respectively, will provide the necessary final proof[1].

It is the potential for normal control of glucose metabolism which provides the rationale for transplantation of the endocrine pancreas in the type I diabetic. Early retinal and renal changes seen in rodents with artificially induced diabetes can be reversed with successful transplantation of the endocrine pancreas either as a vascularized organ graft or as an isolated islet graft. In man, cadaver kidneys with evidence of diabetic nephropathy which are transplanted into normal recipients have shown regression of the renal changes on subsequent biopsy. Furthermore, patients who have been given a renal transplant because of diabetic nephropathy and who have later developed histological evidence of diabetic nephropathy in the transplanted kidney have shown regression of these changes after a successful pancreatic graft. However, in patients who have had a successful pancreatic transplant for several years, evidence regarding the progress of secondary complications is conflicting: indeed, there are reports that retinopathy improves[2], or gets worse[3], and that neuropathy remains unchanged[4]. However there is some evidence that the basal membrane thickness of glomeruli in transplanted kidneys does not increase in diabetic patients receiving a combined kidney and pancreatic transplant, as opposed to a kidney transplant only[5]. Thus, to influence the angiopathic complications of diabetes, transplantation of the endocrine pancreas may have to be performed relatively early and before these vascular changes have become irreversible. Herein lies the problem, for if this were to be done the procedure and the subsequent immunosuppressive therapy would have to be relatively free from complications or side effects.

The possible approaches are either transplantation of the pancreas as a vascularized graft using the whole organ or the body and tail (the only clinical approach available at present), or transplantation of the endocrine tissue only, in the form of fetal pancreas or isolated adult islets. Transplantation of the whole organ with the duodenum together with a kidney transplant was first carried out in Minneapolis in 1966 by Lillehei and colleagues in a number of diabetic patients with end-stage renal failure[6]. The results were understandably poor, although they demonstrated that it was possible to render a type I diabetic patient insulin independent. Interest in pancreatic transplantation waned until Dubernard *et al.* described a technique of blocking the pancreatic duct with neoprene to avoid the potential complications of the exocrine drainage[7]. The renewed interest in pancreatic grafting received an additional impetus after cyclosporine became available; over the last 10 years, 1200 transplants have been performed and just under 300 were performed in 1987. The fact that the First International Congress on Pancreatic Transplantation has just been held in Stockholm, with an attendance of 400 delegates, shows the rapidly increasing interest in this the Cinderella of transplantation.

A number of techniques are being used to transplant the pancreas as a vascularized graft. The duct is either obstructed with a variety of glues, such as neoprene, or prolamine, or it is drained into a Roux-en-Y loop of small bowel, ureter, bladder or stomach. The more recent use of the whole organ rather than a segment of distal pancreas represents an attempt to increase the islet cell mass transplanted. The pancreatic blood vessels (the splenic artery and vein in a segmental graft or the coeliac artery with the superior mesenteric artery on an aortic patch and portal vein in the case of a whole organ graft) are anastomosed to the iliac vessels. In the technique devised by Calne the splenic vessels of the segment are anastomosed to the splenic vessels of the recipient with drainage of the duct into the stomach. Sutherland and his colleagues have used the inferior mesenteric vessels with enteric drainage of the duct. These two techniques provide the theoretical advantage of a physiological delivery of insulin into

0007–1323/88/070627–03$3 00

the portal, rather than the systemic, system and do not produce hyperinsulinaemia which might influence the course of the secondary complications.

At present there is no convincing evidence that any one technique is superior: all carry a significant morbidity. However, transplantation of the whole organ with a segment of duodenum and drainage into the bladder is becoming the most popular method. The major complications are leakage of exocrine secretions, pancreatitis and vascular thrombosis. The International Registry held by Sutherland in Minneapolis shows an overall patient and graft survival rate at 1 year of around 80 per cent and 50 per cent respectively since 1983. However individual units do have better results, with some reporting 1 year graft survival rates of over 70 per cent in relatively small numbers of patients[8]. A successful pancreatic transplant renders the diabetic patient insulin independent (the only really valid criterion of success) and maintains an essentially normal 24-h glucose profile. The physiological response to glucose challenge is more likely to be normal when the venous drainage of the graft is into the portal system.

Rejection of the pancreas is no less of a problem than with other organs. Surprisingly, the pancreas may be rejected without this being evident in the kidney (and *vice versa*), despite both organs being from the same donor. Another potential problem is recurrence of the disease—type I diabetes being an auto-immune disorder. This has certainly occurred in several identical twin transplants in Minneapolis when immunosuppression was not used. Recurrence of diabetes may be prevented by immunosuppression, or indeed if the auto-immune response is restricted by the major histocompatibility complex (MHC) (i.e. the auto-immune response which attacks the patients' own pancreatic islets can only recognize the target antigen in association with self MHC) then this may not be a major problem except in HLA identical transplants. It also suggests that it may be preferable to transplant an HLA mismatched pancreas to reduce the possibility of recurrence while, however, increasing the likelihood of rejection.

The advantages of transplantation of the endocrine tissue only, either as isolated islets or fetal pancreas, are several. The procedure would be relatively minor and safe, it would allow immunomodulation of the graft and long-term preservation of islet tissue and, in the case of fetal pancreas, it would allow replication of B cells either in culture before transplantation or after transplantation. Rejection of isolated islets or fetal pancreas is no less of a problem than is rejection of the vascularized organ. However, the immunogenicity of both fetal pancreas and adult islets can be reduced in certain experimental rodent models by culture at room temperature for several days or treatment with monoclonal antibodies directed at passenger leucocytes in the islet before transplantation, on the basis that these are the cells primarily responsible for induction of the immune response in the recipient[9]. These approaches would be applicable to clinical practice, if they can be shown to be valid in larger mammals.

A major problem which has hindered progress in transplantation of isolated adult islets in man is the lack of a technique to obtain islets of adequate purity and in sufficient numbers. The technique used in rodents is not applicable to the larger more fibrotic human pancreas. However, the description of a greatly improved technique to obtain islets from human pancreas has renewed interest in this approach[10], and preliminary attempts to transplant islets in the USA have shown some evidence of temporary function. This method has allowed successful islet autografts in primates[11], but improvements are still being made in the isolation technique[12,13], and further clinical trials can be anticipated in the near future.

Although fetal pancreas transplantation provides both logistic and ethical problems of supply, fetal pancreas has the potential to replicate and is easily maintained in culture (the exocrine fetal tissue fails to develop both *in vitro* and *in vivo*). A single fetal pancreas can reverse diabetes in the rat after a period of some weeks. Several attempts have been made to transplant fetal pancreas in the clinical field, with 12 successful transplants out of over 300 being reported from China (Hu, personal communication). There are two or three cases in the West where some evidence of partial function has been seen, such as an increase in serum C peptide levels. Although both islet and fetal pancreas transplantation need considerable further development, progress is sufficiently encouraging to suggest that successful transplantation can be achieved in the not too distant future.

The major problem of pancreatic transplantation is that it is performed not to save life but in the expectation that it will halt the progress of the angiopathic complications of diabetes and improve the quality of life of the insulin dependent patient. The morbidity associated with segmental or whole organ pancreatic transplantation precludes its application to patients other than diabetics with renal failure who require a kidney transplant and so need immunosuppression. Furthermore, pancreatic graft survival is poorer when the pancreas alone is transplanted as opposed to the more usual combined transplantation of kidney and pancreas from the same donor.

Pancreatic transplantation should still be regarded very much as an experimental procedure and not as another organ for transplant units to add to their transplant shopping list. If successful pancreatic islet or fetal pancreas transplantation can be achieved, and if rejection of the graft can be prevented in a manner that is relatively free from side effects and complications, then at last one would be in a position to transplant the juvenile onset diabetic at an early stage with the expectation of curing the diabetes and so preventing the later development of its angiopathic complications. If this were to be achieved, then the logistic problems of supply would immediately be insoluble, remembering that for example there are 250 000 insulin dependent diabetics in the UK alone. However it would seem reasonable to cross one bridge at a time!

P. J. Morris

Nuffield Department of Surgery
University of Oxford
UK

1 The DCCT Research Group. Are continuing studies of metabolic control and microvascular complications in insulin-dependent diabetes mellitus justified? *New Engl J Med* 1988, **318**. 246–50
2. Ulbig M, Kampik A, Landgraf R, Land W. The influence of combined pancreatic and renal transplantation on advanced diabetic retinopathy. *Transplant Prac* 1987; **19**. 3554–6
3. Ramsay RC, Goetz FC, Sutherland DER *et al.* Progression of diabetic nephropathy after pancreas transplantation for insulin dependent diabetes mellitus. *New Engl J Med* 1988, **318**: 208–14.
4 Solders G, Wilczek H, Gunnarsson R, Tyden G, Persson A, Groth CG. Effects of combined pancreatic and renal transplantation on diabetic neuropathy. a two-year follow-up study. *Lancet* 1987; **ii**: 1232–4.
5 Bohman SO, Wilczek H, Tyden G, Jaremko G, Lundgren G, Groth CG. Recurrent diabetic nephropathy in renal allografts placed in diabetic patients and protective effect of simultaneous pancreatic transplantation. *Transplant Proc* 1987; **19** 2290–3.
6. Lillehei RC, Simmons RL, Najarian JS *et al.* Pancreatico-duodenal allotransplantation. experimental and clinical experience. *Ann Surg* 1970; **172**. 405–36.
7. Dubernard JM, Traeger J, Wegra P, Touraine JL, Tranchant D, Blanc-Brunat N A new method of preparation of segmental pancreatic grafts for transplantation· trials in dogs and in man. *Surgery* 1978; **84**: 633–9.
8. Sollinger HW, Stratta RJ, Kalayoglu M, Pirsch JD, Belzer FO Pancreas transplantation with pancreatic cystostomy and quadruple immunosuppression. *Surgery* 1987; **102**: 674–8.
9. Austyn JM, Steinman RM. The passenger leukocyte: a fresh look. In. Morris PJ, Tilney NL, eds. *Transplantation Reviews*. New York: Saunders, 1988· (in press).
10. Gray DWR, McShane P, Grant A, Morris PJ. A method for isolation of islets of Langerhans from the human pancreas. *Diabetes* 1984; **35**: 1055–61.
11. Sutton R, Gray DW, Burnett M *et al.* Metabolic function of intraportal and intrasplenic islet autografts in the cynomolgus monkey *Diabetes* 1988, **39**: (in press).
12. Ricordi C, Scharp DW, Lacy PE. Automated islet isolation from the human pancreas. *Diabetes* 1988; **39**: (in press).
13. Lake SP, Bassett PD, Larkins A *et al.* Large scale purification of human islets utilising a discontinuous albumin gradient on an IBM 2991 cell separation. *Diabetes* 1988; **39**: (in press).

Br. J. Surg. 1988, Vol. 75, July,
630–631

Variations in surgical practice: welcome diversity or disturbing differences

B. Jennett

Institute of Neurological Sciences,
Southern General Hospital,
Glasgow G51 4TF, UK
Correspondence to:
Professor B Jennett

The review examines the variations in surgical practice and assesses the value of surgical audit in quality control and allocation of surgical resources.

Keywords: Surgery, morbidity, quality control, outcome, audit

The last decade has seen the publication of numerous reports of geographical variations in health care—both between countries and within them. Most deal with varying rates for elective surgical operations, the first such paper being on tonsillectomy rates in British school children 50 years ago[1]. Many of the recent studies have been in North America but the WHO now has a European Collaborating Center for regional variations. The activities of surgeons are so readily counted that they are particularly vulnerable when such data become available to managers who are anxious to review the work of their more expensive clinicians. These comparisons have mostly been produced by epidemiologists on the basis of routinely collected statistics, a source that clinicians often mistrust because they have frequently been shown to be incomplete. In any event such information relates only to such crude features as numbers of procedures, numbers on waiting lists, how long patients wait to get into hospital, how long they stay there, and overall case mortality. Of more interest to surgeons are data that pertain to variations in clinical aspects of management. These include the types of investigations or therapies which are used, the kinds of patients which are dealt with (age, diagnosis and severity of disease), the results achieved and complications encountered. Such comparisons involve surgeons in data collection and their conclusions are reported in the surgical journals. However, because these contributions of surgeons do not appear under the masthead of the literature on variations, they are seldom recognized by the *aficionados* of health care variations. It is likely that more data of this kind will become available as more surgeons adopt audit of various kinds. Indeed it is useful to classify information about variations according to the three main types of audit—provision, process and outcome.

Data about *provision* are readily available—if not always accurate. These include the facilities provided to undertake surgery: the numbers of surgeons, anaesthetists, nurses, beds, operating theatres and clinics. Variations in these are usually expressed per unit of population but, if per district or region, there is scope for argument about the *de facto* catchment population served. Several aspects of *process* can be identified: relating to how much is done, what is done, which patients are selected and which surgeons are involved. It is the 'how much' data that can readily be generated from routine statistics, forming the basis of reported variations in population-based rates for different operations, length of waiting lists, and efficiency or performance indicators such as patients per bed, per machine and per surgeon. But data about 'what is done to whom by whom' is more likely to capture the interest of surgeons—as should all aspects of *outcome*. Outcome includes not only immediate survival and improvement but how long such benefits last and what burdens are involved[2]. These burdens include not only death and early complications but incomplete symptom relief and any added disability that is the result of surgery. Some of these are an inevitable consequence of successful surgery (e.g. colostomy, mastectomy, limb amputation). It is variations in *avoidable* deaths, complications and adverse long-term results which should concern surgeons as indicators of their performance.

Surgeons in several specialties in the UK have published data on variations in process and outcome, and in many instances these have led to improvement in the quality of care. Earlam used hospital activity analysis to review patterns of management of oesophageal cancer in North-East Thames and the variations disclosed led to the setting up of an MRC trial[3]. A higher mortality rate for prostatectomy in district hospitals as compared with teaching hospitals has been reported more than once from routine statistics[4,5]. Prospectively collected registers can yield more details and a good example is the UK Cardiac Surgery Register. This has revealed five- to tenfold variations between regions in the rates for different types of operation[6]; it was agreed that mortality and complication rates for different units would not be published, but these are said to have varied considerably. Success rates after renal transplantation have been shown to vary widely between different surgical centres[7]. Considerable variations in the treatment of breast cancer were found when 454 general surgeons in the UK were asked about the kind of operation done and about how patients were selected for postoperative radiotherapy and chemotherapy[8]. Some commentators regarded these variations, as not only unsurprising but even welcome, as evidence that clinical freedom was still alive and well in the NHS. It does, however, seem inherently improbable that patients receiving such widely divergent therapy were all getting optimal care. Audit in one London district revealed that postoperative mortality in one general hospital was higher than in the adjacent teaching hospital; the discovery of this variation led to the establishment of an intensive care unit in the district general hospital[9]. The collaboration of 84 UK surgeons in the bowel cancer project showed a six times variation in the rate of breakdown of the anastomosis, a complication associated with a trebling of mortality and a doubling of the length of stay[10]. The main variable seemed to be the surgeon in charge of the case, not only because of what happened in the operating theatre but because of his particular pre-operative and postoperative regimens. Had

0007–1323/88/070630–02$3 00

all the surgeons obtained the results of the best surgeons, there would have been an annual saving of 450 deaths and £4 million. Prospective study of severe head injuries in three countries showed no better outcome with more aggressive use of certain components of intensive care[11]. However, ensuring that more patients reached specialist neurosurgical care and got there sooner after injury led to improved outcome after operation for intracranial haematoma in one British unit[12].

The organization of surgical services also varies widely but this important aspect of surgical activity is seldom analysed by surgeons themselves. A review of waiting lists revealed wide variations between districts and hospitals for the same specialty, 5 per cent of the districts accounting for 10 per cent of the national list[13]. Most of those who had waited for more than a year were on lists in their own districts and were waiting for one of half a dozen mundane procedures, many of which might have been done as day cases. Nor do long lists consistently correspond to limited resources; some districts with high throughputs and short lists have fewer facilities than others that seem forever to be struggling. Commenting on this report the *Lancet* referred to the frequent stories of patients waiting because their conditions were 'not interesting'; it suggested that there would have to be behavioural modification on the part of doctors before the problem would be solved[14]. A somewhat similar conclusion was reached by Wennberg after years of study of variations in the rates for common elective operations[15]. He found little relationship between these rates and the supply of surgeons or surgical facilities, or the means of paying surgeons; differences were as wide between nearby areas in New England as between different countries[16]. The main influence was the practice style of individual surgeons, their 'surgical signature' as he called it. He pointed out that the decision rules of surgeons are apt to be derived from too much traditional teaching and schools of thought, based on clinical hypotheses that are weak, implicit and frequently untested[17]. But he finds that decisions by physicians and paediatricians about admitting patients to hospitals are equally variable[18].

The most recent evidence about wide variations in the organization of surgical practice comes from the Confidential Enquiry into Perioperative Deaths (CEPOD) in three English regions[19,20]. There were differences between surgeons and anaesthetists, between surgical specialties, and between hospitals and regions. These applied particularly to the degree of supervision and participation on the part of consultant surgeons in decision-making and operating out of hours or on emergencies. Many of the deaths followed operations on patients who were elderly and/or had advanced surgical or other disease, who probably should not have been subjected to surgery. In certain places and specialties, inadequately trained and instructed junior surgeons and anaesthetists were undertaking major operations on critically ill patients with fatal results—although there were no data about how often such endeavours had successful outcomes. There were also large variations in whether or not there are regular meetings about deaths and complications, in the attendance at autopsies, and in the interest that surgeons who had reported deaths to CEPOD showed in the conclusions of its assessors.

In a robust foreword to this report Sir Andrew Kay and Sir Gordon Robson took the view that formal audit was no longer an optional activity for surgical units—it should become a must, at least for those seeking approval for higher training. Moreover audit should involve more than regular meetings to discuss 'interesting' deaths and complications. It should entail reaching conclusions about what happened in all such cases, and then making recommendations about what should be done under similar circumstances next time. It should also include some regular review of all the work of the service, and a record should be kept so that changes in the balance of workload, in practice and in outcome can be recognized. The *Lancet* observed that some surgeons are still sceptical of audit while others offer the excuse of lack of time or resources[19]. It went on to suggest that if health authorities are serious about wanting to encourage their surgeons to improve their quality of care they should provide computers and some clerical support for audit.

Audit is of limited use if there is not a standard by which performance is expected to be judged. Both this and the better supervision of junior staff would be facilitated by the development of clinical guidelines, particularly for clinical situations that may present urgently. These are mostly fairly stereotyped and it should not be difficult to agree on outlines of management, including clear indications of when more senior or specialized advice should be sought. These should also give guidance about the value of postponing immediate intervention whenever possible, and also about when a decision to withhold surgery might be appropriate[21]. In this way surgeons would be moving towards making their practice more of a managed event, a recommendation made in response to the challenge about variations in waiting list management[22]. Drawing up guidelines requires surgeons to declare their objectives and methods and to express their disagreements explicitly. This can be uncomfortable and it takes time. But if it led to more consistent and more compassionate care, as well as to better use of surgical resources, the time and effort would have been worthwhile.

References

1. Glover JA. The incidence of tonsillectomy in school children *Proc R Soc Med* 1938; **31**: 95–112.
2. Jennett B Balancing benefits and burdens in surgery *Br Med Bull* 1988; **44**· 499–513.
3. Earlam R. Oesophageal cancer treatment in North-East Thames Region 1981, medical audit using HAA data. *Br Med J* 1984; **288**· 1892–94.
4. Lee JAH, Morrison SL, Morris JN. Fatality from three common surgical conditions in teaching and non-teaching hospitals *Lancet* 1957; **ii**: 785–90.
5. Anon. Second-best prostatectomy *Br Med J* 1980; **i**· 590.
6. English TAH, Bailey AR, Dark JF *et al*. The UK Cardiac Surgical Register 1977–82. *Br Med J* 1984; **289**: 1205–8.
7. Taylor RMR, Ting A, Briggs JD Renal transplantation in the UK and Ireland—the centre effect. *Lancet* 1985; **i**· 789–802.
8. Gazet J-C, Rainsbury RM, Ford HT *et al* Survey of treatment of primary breast cancer in Great Britain. *Br Med J* 1985; **290**. 1793–5.
9. Gilmore OJA, Griffiths NJ, Connolly JC *et al*. Surgical audit, comparison of the workload and results of two hospitals in the same district *Br Med J* 1980, **281**: 1050–2.
10. Fielding LP, Stewart-Brown S, Blesovsky L *et al*. Anastomotic integrity after operations for large-bowel cancer, a multi-centre study. *Br Med J* 1980; **ii**: 411–14.
11. Jennett B, Teasdale G, Fry J *et al*. Treatment for severe head injury *J Neurol Neurosurg Psychiat* 1980; **43** 289–95.
12. Teasdale G, Galbraith S, Murray L *et al*. Management of traumatic intracranial haematoma. *Br Med J* 1982; **285**. 1695–7
13. Davidge M, Harley M, Vickerstaff L *et al*. The anatomy of large inpatient waiting lists. *Lancet* 1987; **i**: 794–6
14. Anon. Down with waiting lists and times. *Lancet* 1987; **i**: 784–5.
15. Wennberg JE. Dealing with medical practice variations, a proposal for action. *Health Affairs* 1984; **3**: 6–32.
16. McPherson K, Wennberg JE, Hovind OB *et al* Small area variations in the use of common surgical procedures· an international comparison of New England, England and Norway. *N Engl J Med* 1982; **307**: 1310–14
17. Wennberg JE, Barnes BA, Zubkoff M Professional uncertainty and the problem of supplier induced demand. *Soc Sci Med* 1982, **16**: 811–24.
18. Wennberg JE, Freeman JL, Culp WJ. Are hospital services rationed in New Haven or over-utilised in Boston? *Lancet* 1987; **i** 1185–9.
19. Lunn JN, Devlin HB Lessons from the Confidential Enquiry into Perioperative Deaths in three NHS regions *Lancet* 1987; **ii**: 1384–6.
20. Anon. Accounting for perioperative deaths *Lancet* 1987, **ii** 1369–71
21. Jennett B. Decisions to limit treatment. *Lancet* 1987, **ii**: 787–9.
22. Jennett B. Waiting lists: a surgeon's response *Lancet* 1987; **i**: 796–7.

Paper accepted 26 February 1988

Br. J. Surg. 1988, Vol. 75, July,
632–636

Traumatic retroperitoneal venous haemorrhage

S. R. G. Smith

St. Mary's Hospital, Praed Street,
London W2 1NY, UK
Correspondence to:
Mr S R G. Smith, Selly Oak
Hospital, Birmingham B29 6JD,
UK

Vena caval injury is rare in the UK, but changes in society suggest that it may become more frequent. The problem is always unexpected and presents a major surgical challenge. Modern techniques have led to a substantial improvement in survival so that most patients with an infrarenal injury should now survive but only with prompt, effective treatment. In this review the problems and techniques of surgical management are illustrated by three cases of traumatic injury and two of peroperative accidents.

Keywords: Venous haemorrhage, retroperitoneal, trauma

In the UK, trauma to the major retroperitoneal veins appears to be rare. Current trends in civilian life[1–3] suggest that this injury is likely to become more frequent, as it did in North America during the 1970s[4,5]. Injury to these veins from whatever cause almost always presents unexpectedly and constitutes a major challenge to the surgeon and to the support teams of his hospital. Experience has shown that awareness of the problems can influence survival[6]. This review was prompted by the experience of three cases presenting in a district general hospital.

Incidence statistics

Most of the data on traumatic injury of the inferior vena cava (IVC) and iliac veins come from large cities in the USA where the relative incidence of the common causes has not changed over 30 years. Firearm wounds account for 74 per cent of the injuries, stabbing 15 per cent, and blunt trauma, 11 per cent[4,5,7,8]. Trauma to retroperitoneal veins accounts for between 10 and 20 per cent of abdominal vascular injuries[9–11], affects young men and has a propensity to occur on Friday and Saturday nights. Even in the USA, where series as large as 301 cases[4] have been reported, the injury is relatively uncommon. A recent 5-year survey in Denver found IVC injury in 10 per cent of 268 laparotomies for gunshot wounds but in only 3 per cent of 243 carried out for stab wounds or 271 performed for blunt trauma[7].

In the UK most cases will be due to stab wounds and blunt trauma. There are now nearly 1 000 000 private licencees for firearms in England and Wales (*Table 1*), a modest increase since 1980. The actual number of guns in circulation, however, may be two to three times greater[1–3]. There has been a steady increase, particularly since 1980, in the number of reported injuries involving weapons[3] and carrying knives has become fashionable.

In addition to external trauma a number of cases will present to the surgeon as accidents during the course of surgical procedures. Two illustrative cases are presented later.

Factors influencing survival

In the 1950s trauma to the major retroperitoneal veins was universally fatal, with 36 per cent of patients being dead on arrival at hospital[12]. Modern on-site accident care with trained paramedical teams and blood volume replacement, rapid evacuation to hospital and current vascular surgical techniques have reduced the mortality to between 30 per cent and 53 per cent of live admissions[4,5,7,8]. In Denver, 85 per cent of patients were admitted within 35 min of injury, a similar statistic to that achieved for violent injuries in Belfast[7,13]. As a result more patients have arrived at hospital alive but, despite first aid, nearly half were shocked ($BP < 90$ mmHg) on admission, a factor significantly influencing survival[4,6,7]. Haemorrhage accounts for most early deaths.

Although the overall mortality of IVC trauma is high, certain anatomical subgroups fare better (*Table 2*)[4,5,7,8]. Between 25 and 68 per cent (mean 57 per cent) of injuries occur at or above the level of the renal veins. Retrohepatic rupture carries the highest mortality which reflects not only the surgical inaccessibility but also the associated injuries and severe haemorrhage. The injuries are frequently so severe as to be incompatible with life. In blunt liver trauma only about 12 per cent of patients sustain injury to the IVC[14–16]. When injury occurs below the liver, the mortality is much lower except at the large venous junctions (iliocaval and renocaval) where control of haemorrhage is more difficult. The lowest mortality, one out of twenty-seven cases (4 per cent), has been achieved with infrarenal injuries so, with modern care, most of these patients should now survive[7].

The other determinants of survival are the cause of the injury (*Table 3*)[4,6,8], active IVC bleeding at the time of operation[4,5,7,8], an injury to surgery interval greater than 1·5 h[6,7], and the associated injuries. Mortality rate is proportional to the number of

Table 1 *Firearm statistics, England and Wales*[2,3]

	1975	1980	1985
Shotgun licencees		781 854	819 333
Licensed firearms (pistols and rifles)		168 047	160 385
Firearm injuries			
Fatal	46	24	45
Serious	228	252	398
Firearm offences (excluding air weapons)	1361	1555	3362

Table 2 *Incidence and mortality of inferior vena cava trauma (from 435 reported cases*[4,5,7,8]*)*

Sites of injury	Percentage occurrence (average)	Percentage mortality (range)
Retrohepatic	22	70
Renal/suprarenal	57	45–66
Infrarenal (all)	43	16–27
Isolated infrarenal		4–20

additional vascular injuries and to a lesser extent to visceral injuries. Overall, 39 per cent of patients have other vascular injuries which include injury to the portal vein and aorta (11 per cent), major gastrointestinal vessels (9 per cent), mesenteric veins (7 per cent), iliac vein (5 per cent) and artery (3 per cent), and hepatic veins (4 per cent). The liver is the most frequently involved viscus followed by the small bowel, pancreas and colon. All intra-abdominal/pelvic organs have been injured at some time as have the heart, lung and oesophagus. Compared with the early death rate from haemorrhage, late deaths due to sepsis and organ failure are relatively uncommon, averaging 5 per cent of live admissions[4,6–8].

Following violent trauma such as high-speed road accidents and firearm wounds the evidence of massive blood loss and the need for operation are generally clear. However, resuscitation is an essential pre-operative step[4,6,16]. Several centres in the USA have reported the use of emergency room left thoracotomy and aortic cross clamping for moribund patients but this has not resulted in improved survival in these severely injured patients[4,7]. That they have reached hospital alive reflects the efficiency of the specialist rescue services. In contrast, the injury may present more insidiously. The techniques of surgical repair are illustrated in the following cases.

Cases of traumatic rupture

Case 1

A man aged 37 years was stabbed abdominally with a bread knife. Mild shock consistent with herniation of 1 m of small bowel was corrected with 1 litre of saline. During preparation for theatre he vomited a small quantity of blood and became shocked. At laparotomy free intraperitoneal blood was found to be emanating from jejunal and mesenteric lacerations. A small retroperitoneal haematoma expanded rapidly while the bowel was being repaired. The knife had traversed the duodenum and lacerated the IVC and the right renal vein and artery (*Figure 1a*). For expediency the right kidney was sacrificed. The IVC was repaired with 4/0 Prolene (Ethicon Ltd., UK), using a transluminal approach to the posterior laceration. The postoperative course was stormy but without major mishap apart from a late wound dehiscence. There was no clinical evidence of vena caval obstruction. Blood transfusion of 20 units was required.

Table 3 *Mortality related to cause of injury (averaged from 393 reported cases*[4,6,8]*)*

Cause	Percentage occurrence	Percentage mortality
Blunt injury	11	85
Stabbing	15	10
Shotgun	74	58
Gunshot		25

Case 2

A 72-year-old driver suffered blunt trauma to his right side when his car was struck by another, square on the off-side. Conscious on admission, he was mildly shocked with right ribs 3–11 fractured but without significant haemothorax. The abdomen was tender and lavage confirmed free intraperitoneal blood. He was known to have ischaemic heart disease and there was clinical evidence of a right postphlebitic limb. A previous right deep vein thrombosis with concomitant swelling of the left leg was later confirmed.

After resuscitation, laparotomy revealed a small amount of free blood arising from a 5 cm fracture of the free edge of the liver. The dome of the liver and diaphragm were uninjured but a right retroperitoneal haematoma was noted. During liver repair the haematoma expanded rapidly. The infrarenal vena cava had been shattered (*Figure 1b*). The right posterior wall was calcified and the lumen replaced by the typical matrix of venous recanalization. The changes extended down the right common iliac vein.

The vena cava was oversewn flush with the renal veins and lumbar tributaries under-run. Distally the vessels were too friable to suture and control was obtained by sewing buttresses of rectus sheath and muscle (TEFLON® (Du pont, UK) buttresses were not available) on to the iliopsoas fascia. Postoperatively he was ventilated and leg swelling was controlled by intermittent compression boots. His condition gradually deteriorated, with poor cardiac output, and he died 10 days later. His renal function initially was satisfactory but later deteriorated. Total blood transfusion of 16 units was required.

Case 3

A motor cyclist, aged 20 years, was thrown forwards after a collision at 20 mph. He received fractures to the left upper arm and left lower leg (compound fracture) but no apparent trunk, pelvic girdle or head injury. He suffered cardiovascular collapse during manipulation of his fractures under general anaesthesia.

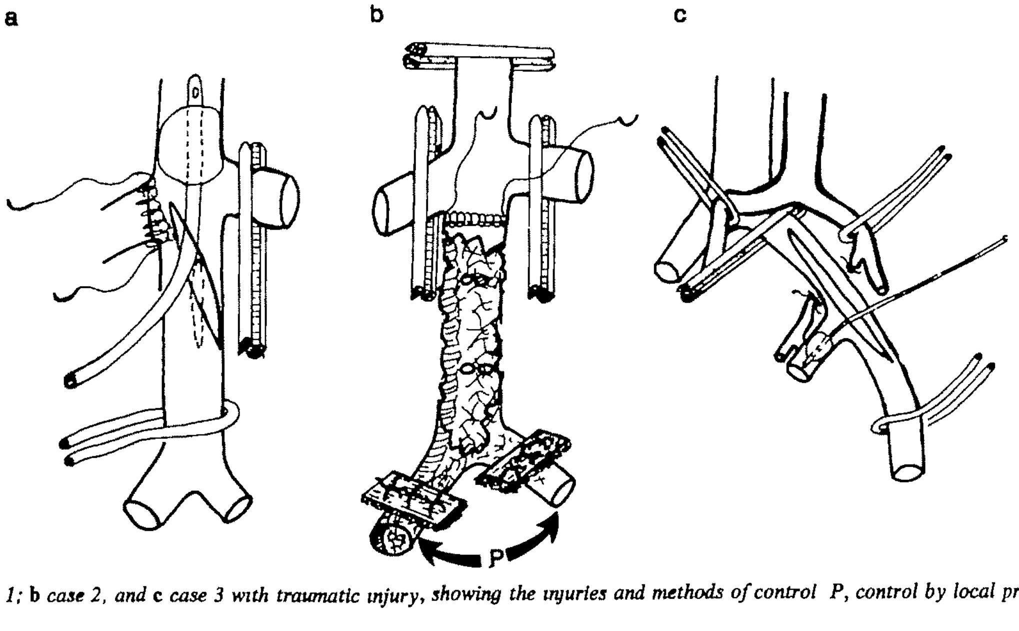


Figure 1 a *Case 1;* b *case 2, and* c *case 3 with traumatic injury, showing the injuries and methods of control P, control by local pressure*

Peritoneal lavage confirmed free intraperitoneal blood and a 4 cm tear of the lower border of the liver was found at laparotomy. The major blood loss was into a large expanding haematoma in the left iliac fossa and pelvis. Mobilization of the left colon confirmed a normal aorta and left kidney. On lifting the sigmoid mesentery the haematoma became unstable with rapid blood loss from a long anteromedial tear of the common and external iliac veins (*Figure 1c*). After division of the left internal iliac artery for access the vein was repaired with 4/0 Prolene. Postoperatively he made an uneventful recovery without leg swelling and had free phasic flow on Doppler ultrasound. Total transfusion of 14 units was required. The mechanism of injury in this case remains obscure. There was no evidence of sacro-iliac disruption.

On presentation, haemorrhage was not a prominent feature of these cases. The injuries were deceptive due to retroperitoneal tamponade of the low pressure haematomata which expanded, in all three cases, to a size equal to that of a ruptured aortic aneurysm. Resuscitation, raised venous pressure and general anaesthesia with positive pressure ventilation, followed by lowered intraperitoneal pressure due to muscle relaxation and incision, overcame the tamponade. These cases illustrate the large transfusion requirements of this injury[6]. The renovascular injury contributed more to the blood loss than did the liver tears.

Techniques of repair

Repair of the veins is generally straightforward. A continuous suture of fine (4/0) polypropylene can be run along the edge of the wound taking care to evert the edges. Any damaged vein should be excised. A vein patch is required in <10 per cent of cases. About 75 per cent (range 62–88 per cent) of injuries at or below the renal veins can be repaired directly without significant narrowing, that is to <50 per cent diameter[4,5,7]. In case 1 (*Figure 1a*), the anterior wound was enlarged to allow clean cuts of the opposite walls to be sutured by a transluminal approach with little narrowing. Ligation of the IVC should be considered, as in case 2, when a major time-consuming repair would prejudice survival[7,8]. Ligation is not the procedure of choice in view of the long-term consequences[4,17–19], although admittedly these are documented for thrombo-embolic disease. As Rich *et al.* have shown, clean injuries to good calibre veins fare well with direct primary repair[20]. Pulmonary embolism after IVC repair has occurred in <2 per cent of cases and thrombosis is rare[4,7].

The major problems are access and control of haemorrhage. A generous incision and three pairs of hands are essential for exposure, suction and control, and the repair. The whole subhepatic IVC can be exposed by mobilization of the right colon, duodenum and head of pancreas as in cases 1 and 2[4,5,7]. In case 3, the left and sigmoid colons were mobilized which allowed control of the lower aorta and vena cava.

Initial vascular control can be achieved by manual compression and packs. These should be employed until adequate surgical equipment and personnel are mobilized. Similarly a haematoma should not be opened until facilities are available for large transfusions of blood and fresh frozen plasma, the patient is resuscitated, and all other bleeding has been controlled[4,7].

A variety of techniques (*Figure 1*) may be necessary to control brisk bleeding which occurs while the vessels are exposed and controlled. Local pressure with fingers or sponge sticks is safe and frequently adequate. Clamps may tear the veins[4]. Despite inflow and outflow control, bleeding will continue, rapidly at times, from inaccessible and easily torn tributaries which enter the main vessels posteriorly. There is a high risk of further tears while attempting to control these veins. Sidebiting or longitudinal clamps, or even tissue forceps, are excellent for clean simple wounds and have the advantage of controlling collateral bleeding into the lumen.

Remote insertion of occlusion catheters

Intraluminal occlusion balloons inserted via the injury (*Figure 1*) are difficult to position and retain. Occlusion catheters inserted via the long saphenous vein[30], however, are satisfactory and have the advantage of offering some control before exposing the injury. Their use is illustrated in two cases (4 and 5) of surgical trauma (*Figure 2*).

Examples of surgical venous trauma

Case 4

During nephrectomy for tumour a large rent in the IVC occurred at the entry of the right renal vein. Profuse haemorrhage followed which was stemmed by packs but did not stop. With packs in place a venous occlusion catheter, with 43 ml balloon, was inserted via a tributary of the right long saphenous vein in the groin and the balloon positioned below the rent. Manual compression provided proximal control and the vessel was repaired directly.

Case 5

During hip replacement, continuous haemorrhage occurred through the wound and injury to the iliac vein was suspected. Two venous occlusion catheters, with 43 ml and 10 ml balloons, were passed via the trunk of the long saphenous vein into the iliac system before opening the abdomen. The balloons were then sited above and below the injury which was repaired directly.

On completion of the repairs the catheters are deflated, withdrawn and the venotomy ligated. Foley catheters have been used, passed via the femoral vein, but may cause long-term damage[7]. In the technique illustrated, specific venous occlusion catheters (Fogarty) were used to occlude the vein without complication.

It has been questioned whether these low pressure haematomata should be opened[21]. Case 3 is a case in point where the origin of the haematoma was uncertain. As a general rule, above the pelvic brim and in cases of penetrating trauma exploration is indicated in view of the risk of delayed exsanguinating haemorrhage and other injuries. Below the pelvic brim without penetration it may be safer not to explore the haematoma. It should be remembered that there is little correlation between the injury and size of haematoma[4,5,7,8,12,13].

Suprarenal injuries of the inferior vena cava

The suprarenal cava must always be repaired as ligation is poorly tolerated. Access to the vena cava between the renal veins and liver can be gained by fully mobilizing the right colon,

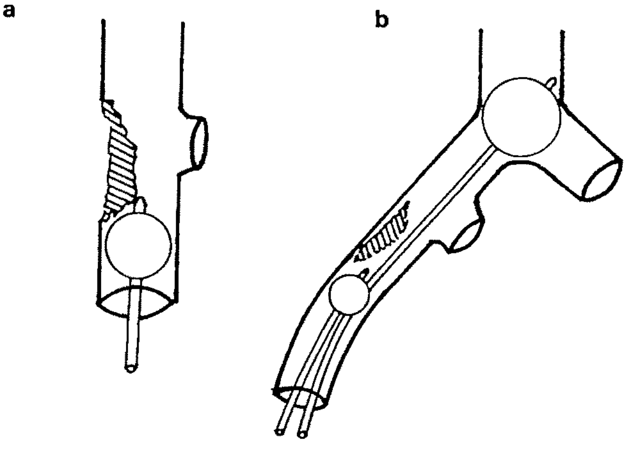


Figure 2 **a** *Case 4 and* **b** *case 5 with surgical trauma, showing the position of venous occlusion catheters inserted via the saphenous vein*

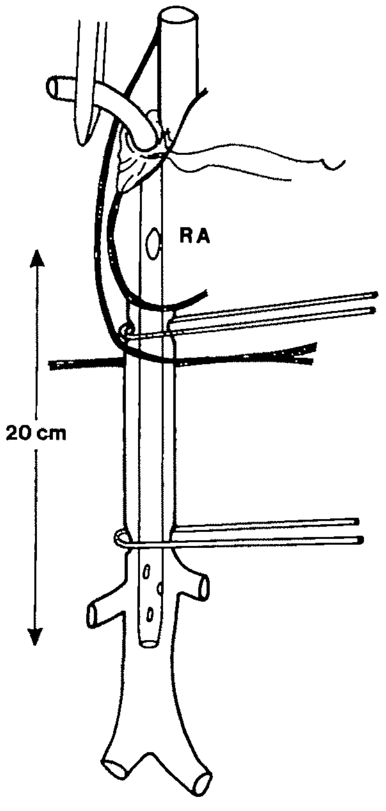


Figure 3 *Atriocaval shunt using a chest drain with a side hole cut for the atrium. The slings are secured by 'snugger' sleeves. RA, right atrium*

duodenum and pancreas. Above this level the liver is rotated downwards and medially by division of the triangular ligaments.

Vascular control before these manoeuvres is critically important as a stable haematoma may be released with uncontrollable haemorrhage. The hepatic inflow can be controlled by Pringle's manoeuvre of cross clamping the porta hepatis[22]. The preferred approach for control of the suprahepatic IVC is by median sternotomy[4,5,23,24] or a direct approach through the diaphragm to the pericardium[25]. Clamping at this level requires massive transfusion to maintain cardiac output[7,16] and may be avoided by right atriocaval shunting. Specific shunts with occlusive balloon sleeves to tamponade the hepatic veins have been designed[26] but are not generally available. A suitable substitute can be prepared from a large (28–36 Ch) chest drain (*Figure 3*). A side hole should be cut 20 cm from the tip to provide drainage into the right atrium. The shunt is inserted through a 2/0 polypropylene purse-string suture in the auricular appendage and filled retrogradely. The technique is well described[4,5,7,16] but carries a risk of air embolus[27].

The best results are obtained when direct repair can be achieved. Rarely, a graft may be required. This can be prepared from saphenous vein as illustrated in *Figure 4*. Prosthetics have equivalent patency[28] but are contra-indicated in the presence of contamination. Despite the application of these techniques there has not been a significant improvement in overall survival from these massive injuries.

The transfusion requirements of vena caval injury are substantial, averaging 4000 ml in survivors[6]. Autotransfusion reduces this requirement and may be beneficial[7]. Cell-saving systems, however, are not widely available and other devices may be unsuitable as the return of unwashed blood can exacerbate coagulopathy[29].

Discussion

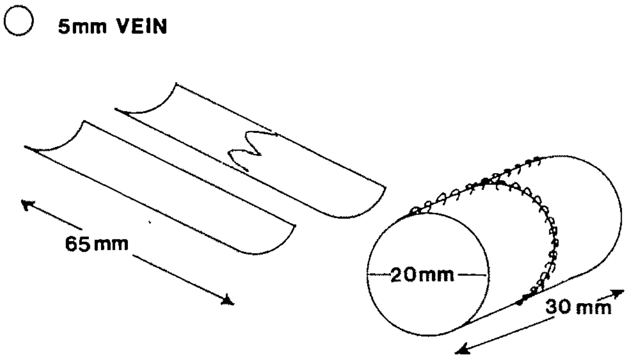


Figure 4 *Construction of a wide calibre vein graft. The total length of vein required is 13 cm*

Traumatic haemorrhage from the major retroperitoneal veins is uncommon but requires urgent skilled surgical attention. In the UK this kind of injury is likely to become more common as a result of the increased use of firearms. In the cases presented there was little initial blood loss but, on abdominal decompression, massive haemorrhage occurred. All surgeons operating for abdominal trauma or in the vicinity of the major retroperitoneal veins should be familiar with techniques for control of haemorrhage and vein suturing. The more complex repairs may require special expertise. Nowadays, provided adequate preparations are made before attempting repair, most patients with subhepatic IVC injury should survive. Survival rates following retrohepatic IVC injury are likely to remain low as, even in receiving hospitals with specialist units, the mortality averages 70 per cent, owing mainly to the enormity of the injury.

Acknowledgements

I thank Mr Paul Stringer, St Albans City Hospital, Mr Nigel Baker, Ashford Hospital, Middlesex, and Miss Averil Mansfield, St. Mary's Hospital, for their permission to report the cases and Miss Mansfield for teaching me her techniques of remote insertion of occlusion catheters.

References

1. Easterman M *File on Four*. 10 June, 1987 BBC Radio 4: Programme number 87NA2223 NHO.
2. Home Office statistics on firearms 1986. *Home Office Statistical Bulletin* 1988; **2**.
3. Criminal statistics England and Wales. HMSO 1985: 43–54.
4. Graham, JM, Mattox KL, Beall AC, DeBakey ME Traumatic injuries of the inferior vena cava. *Arch Surg* 1978; **113**: 413–18
5. Turpin I, State D, Schwartz A. Injuries to the inferior vena cava and their management. *Am J Surg* 1977; **134**: 25–32
6. Halpern NB, Aldrete JS. Factors influencing mortality from injuries to the abdominal aorta and inferior vena cava *Am J Surg* 1979; **137**: 384–8.
7. Millikan JS, Moore EE, Cogbill TH, Kashuk JL. Inferior vena cava injuries—a continuing challenge. *J Trauma* 1983; **23**: 207–12.
8. Duke JH, Jones RC, Shires GT. Management of injuries to the inferior vena cava. *Am J Surg* 1965, **110**: 759–63.
9. Cohen D, Johansen K, Cottingham K, Clayson K, Simonowitz D. Trauma to major visceral veins. An underemphasised cause of accident mortality. *J Trauma* 1980, **20**. 928–32.
10. Ekbom GA, Towne JB, Majewski JJ, Woods JH. Intraabdominal vascular trauma—a need for prompt operation. *J Trauma* 1981; **21**: 1040–4.
11. Kelly G, Eiseman B. Civilian vascular injuries. *J Trauma* 1975; **15**: 507–14.
12. Oscher JL, Crawford ES, DeBakey ME Injuries of the vena cava caused by external trauma. *Surgery* 1961; **49** 397–405.
13. Barros D 'Sa AAB A decade of missile induced vascular trauma *Ann R Coll Surg Engl* 1982; **64**: 37–44.
14. Little JM, Williams CW Improved mortality in the management of liver injuries. *Br J Surg* 1969; **56**: 603–12.
15. Blumgart LH, Vajrabukka T Injuries to the liver, analysis of 20 cases. *Br Med J* 1972, **1**: 158–64.
16. McMaster P, Tolley M Management of inferior vena cava injury in liver trauma. *Ann R Coll Surg Engl* 1977; **59**: 502–6

17. Piccone VA, Vidal E, Yarnoz M, Glass D, Levene HH. The late results of caval ligation. *Surgery* 1970; **68**: 980–98.
18. Stevens LE, Fitzpatrick WK, Stewart GK, Burdette WJ. Ligation of the inferior vena cava *Arch Surg* 1965; **90**: 578–85.
19. Bernstein EF Operative management of acute venous thromboembolism. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: WB Saunders Co., 1984: 1367–84
20. Rich NN, Hughes CW, Baugh JH. Management of venous injuries. *Ann Surg* 1970; **171**: 724–30.
21. Mattox KL In discussion of Millikan *et al.* (1983)[7] *Am J Surg* 1983; **23**: 211–2.
22. Pringle JH. Notes on the arrest of hepatic haemorrhage due to trauma. *Ann Surg* 1908; **48**. 541–9
23. Miller DR Median sternotomy extension of abdominal incision for hepatic lobectomy *Ann Surg* 1972; **17**: 193–6.
24. Fullen WE, McDonough JJ, Popp MJ *et al.* Sternal splitting approach for major hepatic or retrohepatic vena caval injury. *J. Trauma* 1974; **14**: 903–11.
25. Heaney JP, Jacobson A. Simplified control of upper abdominal haemorrhage from the vena cava. *Surgery* 1978; **78**: 138–41.
26. Pilcher BD, Harman PK, Moore EE. Retrohepatic vena cava balloon shunt introduced via the sapheno-femoral junction. *J Trauma* 1977; **17**: 837–41.
27. Bricker DL, Morton JR, Okies JE *et al.* Surgical management of injuries to the vena cava: changing patterns of injury and newer techniques of repair *J Trauma* 1971; **11**: 725–33.
28. Hiratzka LF, Wright CB. Graft materials in the venous system: recent advances. In: Wright CB, ed. *Vascular Grafting*. Bristol: John Wright 1983: 207–17.
29. Moore EE, Dunn EL, Breslick DL *et al.* Platelet abnormalities associated with massive autotransfusion. *J Trauma* 1980; **20**: 1052–6.
30. Smith SRG, Mansfield AO, Bradley JPW. Remotely inserted venous occlusion catheters for the control of venous haemorrhage. *Ann R Coll Surg Engl* 1988; **70**: 161–2.

Paper accepted 21 January 1988

Review

Br. J. Surg. 1988, Vol. 75, July, 637–640

Management of major colonic haemorrhage

A. R. Berry, W. B. Campbell and M. G. W. Kettlewell

Department of Surgery, John Radcliffe Hospital, Oxford, UK

Correspondence to: Mr A. R. Berry

Major colonic haemorrhage remains a difficult diagnostic and therapeutic problem. We propose that those patients who continue to bleed after resuscitation are best served by immediate laparotomy. High flow antegrade irrigation and intra-operative colonoscopy can then be used to localize the site of bleeding and allow appropriate excisional surgery rather than blind colonic resection.

Keywords: Major colonic bleeding, antegrade colonic irrigation, intra-operative colonoscopy, resection

There is a generally accepted method of management of patients with major upper gastrointestinal haemorrhage, but no comparable plan has yet evolved for the less common problem of severe colonic haemorrhage. This may be because colonic bleeding is less often catastrophic, usually stops spontaneously, and the source of bleeding is less obvious[1–4]. Thirty or more years ago, diverticular disease was presumed to be the cause of most colonic bleeding[5–7] and a barium enema, the only non-operative means of investigation available, seldom demonstrated the site of bleeding, though occasionally it appeared to arrest haemorrhage[8]. Consequently, a variety of surgical procedures, including blind left hemicolectomy and segmental colectomy, were performed in bleeding patients who were known to have diverticular disease[9]. Such a policy, however, was associated with a rebleeding rate of approximately 30 per cent and a mortality rate of 20–40 per cent[1,10–12]. Subsequently, subtotal colectomy was proposed as a more reliable means of preventing further haemorrhage[1,12–14].

Techniques were described to try to localize bleeding sites during an operation which included transillumination of the bowel, performing multiple colotomies[9,15], the use of Doppler probes at operation[16], and applying soft intestinal clamps along the emptied bowel until the segment containing the bleeding lesion was found[7]. Hagihara *et al*[17] claimed that the site of bleeding could be confirmed after resection by examining the bowel immediately, using mucosal compression. Performing a transverse colotomy to identify which side of the colon is bleeding or a transverse colostomy to divert faeces away from a presumed source of bleeding in the left colon was of occasional value[18,19]. Even after laparotomy and the use of all of these techniques, the source of bleeding remained obscure in as many as 70 per cent of cases[20]. The advent of newer diagnostic methods such as angiography, isotope scanning and colonoscopy demonstrated that severe colonic bleeding had many causes[21] and that the earlier assumption that most cases were due to diverticular disease was incorrect. The causes of acute colonic haemorrhage are shown in *Table 1*.

Most authorities now believe that vascular malformations of the right side of the colon—vascular ectasia[22–24], arteriovenous malformations[25,26] and, more commonly, angiodysplasia[27,28]—are the main causes of serious bleeding in the elderly As many as 13 different vascular disorders of the colon have been described and they can be broadly divided into five categories: arteriovenous malformations, phlebectasia, telangiectasia, haemangioma and connective tissue disorders of blood vessels[29]. As with diverticular disease, however, Steger *et al.*[30] have cautioned that bleeding can occur from a second source in patients with known colonic angiodysplasia. They stressed that the condition can only be diagnosed confidently as the source of blood loss if it is seen to be bleeding actively either at operation, or by endoscopy, or angiographically.

Selective mesenteric angiography was first described for major gastrointestinal bleeding in the early 1960s by Nusbaum and Baum[31–33]. Its pre-operative use to demonstrate the site of bleeding was shown to reduce the incidence of postoperative rebleeding[22], and the need for subtotal colectomy in patients with diverticular disease[34]. Intra-operative angiography for major intestinal bleeding had in fact preceded pre-operative percutaneous angiography[35,36] and, more recently, the technique has been resurrected using image intensification and cannulation of the mesenteric artery[37,38]. Athanasoulis *et al.* showed that an intra-arterial injection of Methylene Blue could also demonstrate the bleeding point at operation[39]. For pre-operative mesenteric angiography to demonstrate the source of haemorrhage, the patient must be bleeding at a rate of at least 0·5–1·0 ml/min at the time of investigation[37,40,41]. The ideal is to perform three-vessel angiography (coeliac, superior and inferior mesenteric arteries) after resuscitation but within 4 h of emergency hospital admission[41,42].

In patients who are not bleeding at a sufficient rate for angiography to demonstrate the site of bleeding it may be identified by radio-isotope scintiscanning. Alavi *et al.* and other authors showed that $^{99\mathrm{m}}$Tc sulphur colloid scanning was more sensitive than angiography, being able to detect bleeding rates as low as 0.05–0.1 ml/min[43–45]. The problem with isotope scanning has been the relatively poor resolution. $^{99\mathrm{m}}$Tc sulphur colloid is cleared by the liver and spleen and images from these organis cause confusion when the bleeding source is in the upper abdomen. The introduction of $^{99\mathrm{m}}$Tc albumen was an alternative[46], but the preferred technique is to use $^{99\mathrm{m}}$Tc-labelled red blood cells which have a longer half-life in the blood stream and are therefore more helpful in demonstrating the source of intermittent bleeding[47]. Winzelberg *et al.*[48] and Olsen *et al.*[49] concluded that scanning with $^{99\mathrm{m}}$Tc-labelled red cells was more sensitive than angiography in differentiating right from left sided colonic bleeding. In spite of the lower resolution, they felt that isotope scanning should precede angiography, it being non-invasive and more sensitive. Other authors have proposed this technique as the first choice investigation in active colonic bleeding[50,51]. In 5 patients who required emergency surgery (out of 53 studied) a $^{99\mathrm{m}}$Tc-labelled red blood cell scan located the site of bleeding in all cases[52] and this would seem to be the isotope of choice at the present time[53]. Olsen *et al.* pointed out that scintigraphy is of little value once bleeding has stopped[49].

The use of colonoscopy was first reported in patients with acute lower intestinal bleeding by Deyhle and colleagues in the early 1970s[54]. Though the procedure was particularly helpful in patients with intermittent bleeding, subsequent studies showed it to be less successful in patients with massive haemorrhage when adequate inspection proved impossible[55,56]. Forde[57] had more success in acute bleeding using a pulsatile irrigation system with a double channel endoscope, but emphasized the

0007–1323/88/070637–04$3.00

Table 1 *Reported causes of lower gastrointestinal bleeding*

Cause of bleeding	Frequency (%)*	Particular age group at risk	Reference
Diverticular disease	23–55	>60 years	3, 21, 80, 81
Angiodysplasia etc	1–20	>60 years	2, 3, 21, 22, 25, 80–83
Carcinoma	6–10	>50 years	3, 21, 80, 81, 84
Polyps	7–15	Any age	80–83
Inflammatory bowel disease	3–8	Young to middle-aged	3, 21, 81–83, 85–87
Meckel's/small bowel	5–10	Young to middle-aged	78
Trauma/impaction/iatrogenic	1–5	Any age	3, 4, 88, 89
Radiation enteritis	1–7	Any age	21, 81, 91
Ischaemic colitis	1–3	>60 years	80–83
Anticoagulant therapy	1–5	Any age	97
Haemorrhoids/fissures	1	Any age	3, 4
Colonic varices	Rare	Middle-aged to elderly	92–94
Pseudomembranous colitis	Rare	Any age	95
Solitary rectal ulcer	Rare	Young to middle-aged	96
Small solitary colonic ulcer, large submucosal artery	Rare	—	98
Aorto-enteric fistula (postaortic surgery)	Increasing	>60 years	99

* An attempt has been made to compensate for the differing inclusion criteria used in the various studies quoted

technical difficulty of the procedure and the risk of perforation. Vellacott[58] reported a diagnostic success rate of 54 per cent using early colonoscopy in patients with severe continued bleeding. One of his patients, however, developed septicaemia following colonoscopy, again demonstrating the potential dangers. It is now generally accepted that colonoscopy is the investigation of choice, once bleeding has ceased, because it is the most sensitive at detecting mucosal lesions[59].

Until recently, intra-operative colonoscopy, although quite widely practised[23,59–62], had been unhelpful in the difficult situation of massive bleeding, even using constant irrigation[23,60,61]. In 1983 Radcliffe and Dudley[63] described the simple technique of caecal intubation and high flow antegrade irrigation of the colon to prepare the obstructed bowel for resection and primary anastomosis, and we believe that this important manoeuvre has led to a major advance in the management of this difficult group of patients with massive colonic bleeding who need urgent resection. When used in combination with intra-operative colonoscopy it offers the best chance of identifying the main source of bleeding and therefore limiting the extent of colonic resection[62,64,65]. Further modifications of the technique have enabled the procedure to be completed with greater speed and less contamination[66–68]. In fact when the lavage is performed in this situation, there is very little contamination because the colon is not divided and the effluent is drained through the anus. If necessary, the irrigation can be continued during the endoscopy. The other additional benefit is that the bowel is perfectly prepared for subsequent resection and anastomosis.

With the evolution of these more sophisticated techniques of investigation and accurate localization of colonic bleeding, our perception of the ideal surgical treatment has changed and there is now little place for blind subtotal colectomy[69], particularly in view of the 60 per cent incidence of rebleeding and the associated mortality[70]. Angiography and endoscopy not only increase the diagnostic rate, but both also offer means of non-operative treatment. Intra-arterial vasopressin[71–73] or embolization[74,75] can be used to arrest haemorrhage identified at angiography, though the risk of intestinal infarction is a drawback[37]. Colonoscopy, on the other hand, may enable an area of bleeding angiodysplasia to be treated by electrocoagulation[59] or laser ablation[76] with little risk of perforation.

How then should we manage the patient with severe colonic haemorrhage, and is there a useful algorithm for treatment? Firstly, it is essential to exclude any haematological or coagulation abnormality which may predispose to bleeding. A source of upper gastrointestinal blood loss should then be excluded by naso-gastric aspiration or by oesophagogastroduodenoscopy, and anal and low rectal bleeding should be excluded by proctoscopy and rigid sigmoidoscopy. This having been done, recent practice in massive haemorrhage has been to try to establish a pre-operative diagnosis (or at least the site of blood loss) usually by emergency angiography[59,77]. This approach has been advocated by Thompson *et al.*[78], although they emphasized the difficulties involved and the need for an experienced radiologist to perform the examination. In our hospital, even with such expertise, angiography has not helped in management. Furthermore, some patients have been at serious risk from continued blood loss in a situation where

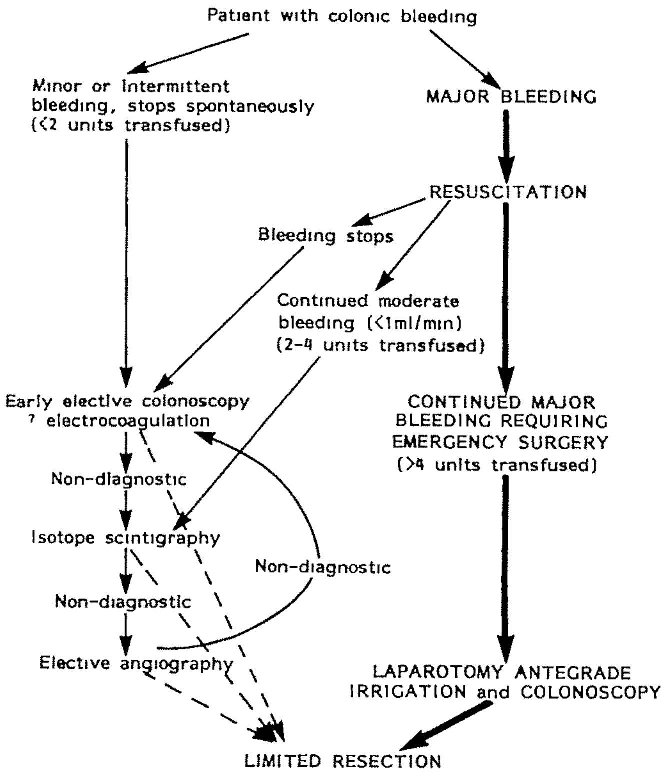

Patient with colonic bleeding
Minor or intermittent bleeding, stops spontaneously (<2 units transfused)
MAJOR BLEEDING
RESUSCITATION
Bleeding stops
Continued moderate bleeding (<1ml/min) (2-4 units transfused)
Early elective colonoscopy ? electrocoagulation
CONTINUED MAJOR BLEEDING REQUIRING EMERGENCY SURGERY (>4 units transfused)
Non-diagnostic
Isotope scintigraphy
Non-diagnostic
Non-diagnostic
Elective angiography
LAPAROTOMY ANTEGRADE IRRIGATION and COLONOSCOPY
LIMITED RESECTION

Figure 1 *Algorithm for the management of patients with major colonic haemorrhage*

monitoring and supervision can be difficult, and during a prolonged procedure (mean length of time 90 min)[79]. The decision to operate on a patient is a clinical one governed by the amount of blood transfused and the rate of continued bleeding. If bleeding is severe enough to merit emergency surgery, angiography is unlikely to arrest haemorrhage, is no better at identifying the site of bleeding than intra-operative colonoscopy, and is consequently likely to be a dangerous waste of time. We therefore believe that patients bleeding rapidly are best served by resuscitation and immediate laparotomy with high flow antegrade irrigation and intra-operative colonoscopy, followed by the appropriate excisional surgery[64,79].

In less active haemorrhage or intermittent bleeding, we suggest early colonoscopy in preference to scintigraphy[57,58] as this enables areas of angiodysplasia to be electrocoagulated, while the latter investigation is of less value because of its poorer resolution. We would only advocate the use of $^{99\mathrm{m}}$Tc-labelled red blood cell scintigraphy and mesenteric angiography in the less acute cases when early colonoscopy has failed to identify the source of bleeding, or in the small proportion of patients with active haemorrhage not severe enough to require emergency surgery but in whom pre-operative colonoscopy may be impossible.

Though practice in any hospital depends very much on the local skills that are available, we believe that skilled colonoscopy is more widely available than expert emergency selective mesenteric angiography—a procedure which is performed rarely in most hospitals. In any event, we now propose a plan of management for patients with major colonic haemorrhage which should be applicable in most hospitals (*Figure 1*) and there should no longer be any place in modern surgical practice for blind colonic resection.

References

1 McGuire HH, Haynes BW. Massive haemorrhage from diverticulosis of the colon. *Ann Surg* 1972; **175**: 847–53

2. Nath RL, Sequeira JC, Weitzman AF, Birkett DH, Williams LF. Lower gastrointestinal bleeding, diagnostic approach and management conclusions. *Am J Surg* 1981; **141**. 478–81.

3. Colacchio TA, Forde KA, Patsos TJ, Nunez D. Impact of modern diagnostic methods on the management of active rectal bleeding. *Am J Surg* 1982; **143**: 607–10.

4. Lacey Smith J. Approaches to the problem of lower gastrointestinal bleeding. *Compr Ther* 1984; **10**: 43–50.

5. Young JM, Howarth MB. Massive haemorrhage in diverticulosis: possible explanation of cause. *Ann Surg* 1954; **140**: 128–31.

6. Fraenkel GJ. Rectal bleeding and diverticulitis. *Br J Surg* 1954, **50**: 643–5

7. Maynard EP, Voorhees AB. Arterial haemorrhage from a large bowel diverticulum. *Gastroenterology* 1956; **31**: 210–11.

8. Adams JT. Therapeutic barium enema for massive diverticular bleeding. *Arch Surg* 1970; **101**: 457–60.

9. Stahlgren LH, Ferguson LK. The surgical management of massive melena. *Am J Surg* 1958, **96**: 515–21.

10. Moore RH. Massive melena. *Ann Surg* 1952, **136**: 167–73.

11. Casarella WJ, Kanter IE, Seaman WB. Right sided colonic diverticula as a cause of acute rectal haemorrhage. *New Engl J Surg* 1972, **286**: 450–3.

12 Drapanas T, Pennington DG, Kappelman M, Lindsey ES. Emergency subtotal colectomy—preferred approach to the management of massively bleeding diverticular disease. *Ann Surg* 1973; **177**: 519–26.

13 Moody FG. Rectal bleeding. *New Engl J Med* 1974; **290**: 839–41.

14. Eaton AC. Emergency surgery for acute colonic harmorrhage—a retrospective study. *Br J Surg* 1981; **68**: 109–12.

15. Beychok IA. Precise diagnosis in severe haematochezia. *Arch Surg* 1978; **113**· 634–6.

16. Fowler DC, Fortin D, Wood WG, Pinkerton JA, Koontz PG Intestinal vascular malformations. *Surgery* 1979; **86**: 377–83.

17. Hagihara PF, Sachatello CR, Mattingly SS, Ram M, Griffen WO. Massive rectal bleeding of colonic origin: localisation of the bleeding site. *Surgery* 1982; **92**: 589–97.

18. Foster RL, Fisher RF. Colostomy as emergency treatment of massive melena secondary to diverticulitis *Am Surg* 1954; **20**: 734–38.

19. Noer RJ, Hamilton JE, Williams DJ, Broughton DS. Rectal haemorrhage moderate and severe. *Ann Surg* 1962; **155**: 794–805

20. Retzlaff JA, Hagedorn AB, Bartholomew LG. Abdominal exploration for gastrointestinal bleeding of obscure origin. *JAMA* 1961, **177**: 104–7

21 Giacchino JL, Geis WP, Pickleman JR, Dado DV, Hadcock WE, Freeark RJ. Changing perspectives in massive lower intestinal haemorrhage. *Surgery* 1979; **86**. 368–74.

22. Boley SJ, Sammartano R, Brandt LJ, Sprayregan S. Vascular ectasias of the colon. *Surg Gynecol Obstet* 1979, **149**. 353–9.

23. Mendoza CB, Watne AL. Value of intraoperative colonoscopy in vascular ectasia of the colon. *Ann Surg* 1982; **48**: 153–6

24. Levine DS. Intestinal vascular ectasia *Am J Med* 1984; **76**. 1151–5.

25. Crichlow RN, Mosenthal WT, Speigel PK, House RK. Arteriovenous malformations of the bowel. *Am J Surg* 1975, **129**· 440–6.

26. Moore JD, Thomson NW, Appelman HD, Foley D. Arteriovenous malformations of the gastrotestinal tract. *Arch Surg* 1976; **111**· 381–8

27. Bogokowsky H, Slutzki S, Alan H. Angiodysplasia as a cause of colonic bleeding in the elderly. *Br J Surg* 1979; **66**: 315–16

28. Vallee C, Legmann P, Favriel JM *et al.* Colonic angiodysplasia—clinical, endoscopic, arteriographic signs and histopathological correlations *Eur J Radiol* 1984; **4**· 258–64.

29. Camilleri M, Chadwick VS, Hodgson JF. Vascular anomalies of the gastrointestinal tract. *Hepatogastroenterology* 1984; **31** 149–53.

30. Steger AC, Galland RB, Hemingway A, Wood CB, Spencer J. Gastrointestinal haemorrhage from second source in patients with colonic angiodyplasia. *Br J Surg* 1987; **74**: 726–7.

31. Nusbaum M, Baum S. Radiographic demonstration of unknown sites of gastrointestinal bleeding. *Surgical Forum* 1963; **14**: 374–5

32 Baum S, Nusbaum M, Blakemore WS, Finkelstein AK. The pre-operative radiographic demonstration of intra-abdominal bleeding from undetermined sites by percutaneous selective coeliac and superior mesenteric angiography. *Surgery* 1965; **58**: 797–805.

33. Nusbaum M, Baum S, Blakemore WS, Finkelstein AK Demonstration of intra-abdominal bleeding by selective arteriography *JAMA* 1965; **191**: 389–90.

34 Talman EA, Dixon DS, Gutierrez FE Role of arteriography in rectal haemorrhage due to arteriovenous malformations and diverticulosis. *Ann Surg* 1979; **190**, 203–13.

35. Schobinger R, Blakman G, Lin RK Operative intestinal arteriography. *Acta Radiol* 1957; **48**: 330–6.

36 Margalis AR, Heinbecker P, Bernard HR Operative mesenteric arteriography in the search for the site of bleeding in unexplained gastrointestinal haemorrhage. *Surgery* 1960; **48**: 534–9.

37. Hines JR, Stryker SJ, Nieman HL *et al.* Intraoperative angiography in intestinal angiodysplasia. *Surg Gynecol Obstet* 1981; **152**: 453–9.

38 Sabanathan S, Nag SB. Operative angiography in the management of massive rectal bleeding. *J Roy Coll Surg Ed* 1984; **29**: 96–9.

39. Athanasoulis CA, Moncure AC, Greenfield AJ, Ryan JA, Dodson TF. Intraoperative localisation of small bowel bleeding sites with combined use of angiographic methods and methylene blue injection *Surgery* 1980; **87**: 77–84.

40. Nusbaum M, Baum S, Blakemore WS Clinical experience with the diagnosis and management of gastrointestinal haemorrhage by selective mesenteric catheterisation. *Ann Surg* 1969; **170**: 506–13.

41. Athow AC, Shepard L, Sibson L. Selective visceral angiography for unexplained gastrointestinal bleeding in a district general hospital *Br J Surg* 1985; **72**: 120–2.

42. Bar AH, De Laurentis DA, Parry CE, Keohane RB. Angiography in the management of massive lower gastrointestinal tract haemorrhage. *Surg Gyn Obstet* 1980; **150**: 226–8.

43 Alavi A, Dann RN, Baum S, Biery DN. Scintigraphic detection of acute gastrointestinal bleeding. *Radiology* 1977; **124**: 753–6.

44. Alavi A. Scintigraphic demonstration of acute gastrointestinal bleeding. *Gastrointest Radiol* 1980; **5**: 205–8.

45. Flickinger FW. Location of acute lower gastrointestinal bleeding by Technetium 99m sulphur colloid scan. *J Nucl Med* 1981; **22**· 38–9.

46. Miskowiak J, Nielson SL, Munck O *et al.* Acute gastrointestinal bleeding detected with abdominal scintigraphy using technetium

99m labelled albumin. *Scand J Gastroenterol* 1979; **14**: 389–94.

47. Winzelberg GG, Froelich JW, McKusick KA, Staun HW. Scintigraphic detection of gastrointestinal bleeding a review of current methods. *Am J Gastroenterol* 1983; **78**: 324–7.
48. Winzelberg GG, Froelich JW, McKusick KA *et al.* Radionucleide localization of lower gastrointestinal haemorrhage. *Radiology* 1981; **139**: 465–9.
49. Olsen PR, Neilsen L, Dyrbye M, Hansen LK. Colorectal bleeding localised with gamma camera. *Acta Chir Scand* 1983; **149**: 793–5.
50 Miller RE. Roentgenographic evaluation of gastrointestinal bleeding *JAMA* 1984; **251**: 271.
51. Gupta S, Lunn E, Kingsley S, Prince M, Herrara N Detection of gastrointestinal bleeding by radionuclide scintigraphy *Am J Gastroenterol* 1984, **79**: 26–31
52. Kester RR, Welch JP, Sziklas JP. The ^{99m}Tc-labelled red blood cell scan. *Dis Col Rectum* 1984; **27**: 47–52.
53. Bunker SR, Lull RJ, Tanasescu DE *et al.* Scintigraphy of gastrointestinal haemorrhage—superiority of ^{99m}Tc red blood cells over ^{99m}Tc sulfur colloid. *Am J Gastroenterol* 1984, **143**: 543–8.
54. Deyhle P, Blum AL, Nuesch HJ, Jenny S. Emergency colonoscopy in the management of acute peranal haemorrhage. *Endoscopy* 1974; **6**: 229–32.
55. Wayne JD Colonoscopy in rectal bleeding. *S Afr J Surg* 1976; **14**. 143–9.
56. Shinya H, Cwern M, Wolf G. Colonoscopic diagnosis and management of rectal bleeding. *Surg Clin N Am* 1982; **62**: 897–903.
57. Forde KA. Colonoscopy in acute rectal bleeding. *Gastrointest Endosc* 1981; **27**: 219–20.
58. Vellacott KD. Early endoscopy for acute lower gastrointestinal haemorrhage. *Ann Roy Coll Surg Engl* 1986; **68**: 243–4.
59. Brandt LJ, Boley SJ. The role of colonoscopy in the diagnosis and management of lower intestinal bleeding. *Scand J Gastroent* 1984; **19**(Suppl 102): 61–70.
60. Martin RJ, Forde KA Intraoperative colonoscopy. *Dis Col Rectum* 1979; **22**: 234–7.
61. Bowden TA, Hooks VH, Mansberger AR. Intraoperative gastrointestinal endoscopy. *Ann Surg* 1980; **191**: 680–5.
62. Batch AJG, Pickard RG, DeLacey G. Peroperative colonoscopy in massive rectal bleeding. *Br J Surg* 1981; **68**: 64.
63. Radcliffe AG, Dudley HAF Intraoperative antegrade irrigation of the large intestine. *Surg Gyn Obstet* 1983; **156**: 721–3.
64. Campbell WB, Rhodes M, Kettlewell MGW. Colonoscopy following intraoperative lavage in the management of severe colonic bleeding. *Ann Roy Coll Surg Engl* 1985; **67**: 290–2.
65. Scott HJ, Lane IF, Glynn MJ *et al.* Colonic haemorrhage: a technique for rapid intraoperative bowel preparation and colonoscopy. *Br J Surg* 1986; **73**: 390–1.
66. Simpson AHRW, Thomson WHF. Technical modifications making on table washout easier. *Br J Surg* 1987; **74**: 464
67. Bradnock B. Speeding up colonic lavage. *Br J Surg* 1987; **74**: 464.
68. Munro A, Steele RJC, Logie JRC. Technique for intraoperative colonic irrigation. *Br J Surg* 1987; **74**: 1039–40
69. Editorial—Visions for the blind colectomy. *Gastrointest Endosc* 1981; **27**: 238–9.
70. Gianfrancisco JA, Abcarian H. Pitfalls in the treatment of massive gastrointestinal bleeding with blind subtotal colectomy. *Dis Col Rectum* 1982, **25**: 441–5.
71. Conn HO, Ramsby GR, Storer EH. Selective intra-arterial vasopressin in the treatment of upper gastrointestinal haemorrhage. *Gastroenterology* 1972, **63**. 634–45.
72. Baum S, Athanasoulis CA, Waltman AL Angiographic diagnosis and control of large bowel bleeding. *Dis Col Rectum* 1974; **17**: 447–53
73. Athanasoulis CA, Baum S, Rosch J *et al.* Mesenteric arterial infusions of vasopressin for haemorrhage from colonic diverticulosis. *Am J Surg* 1975; **129**: 212–16.
74. Olcott C, Newton TH, Stoney RJ *et al.* Intraarterial embolisation of arteriovenous malformations. *Surgery* 1976; **79**: 3–12.
75. Lawler G, Bircher M, Spencer J, Hemingway AP, Allison DJ. Embolisation in colonic bleeding. *Br J Radiol* 1985; **58**: 83–4.
76. Fleischer D. Endoscopic laser therapy for gastrointestinal disease. *Arch Int Med* 1984; **144**: 1225–30.
77. Wright HK, Pelliccia O, Higgins EF, Sreenivas V, Gupta A. Controlled semi-elective segmental resection for massive colonic haemorrhage. *Am J Surg* 1980, **139**: 535–8.
78. Thompson JN, Salem RR, Hemingway AP *et al.* Specialised investigation of obscure gastrointestinal bleeding. *Gut* 1987; **28**: 47–51.
79. Cussons PD, Fletcher EWL, Berry AR. A comparison of the value of mesenteric angiography and on-table colonoscopy in massive acute large bowel haemorrhage. *Gut* 1988; **29**: A727
80 Boley SJ, DiBase A, Brandt LI, Sammartano RJ. Lower intestinal bleeding in the elderly. *Am J Surg* 1979; **137**: 57–64.
81. Levinson SL, Powell DW, Callahan WT *et al.* A current approach to rectal bleeding. *J Clin Gastroenterol* 1981; 3(Suppl 1): 9–16.
82. Teague RH, Manning AP, Thornton JR, Salmon PR. Colonoscopy for investigation of unexplained rectal bleeding. *Lancet* 1987; **1**: 907–9.
83. Tedesco FJ, Waye JD, Raskin JB, Morris SJ, Greenwald RA. Colonoscopic evaluation of rectal bleeding. *Ann Int Med* 1978; **89**: 907–9.
84. Kirkpatrick JR. Massive rectal bleeding in the adult. *Dis Colon Rect* 1969; **12**: 248–52.
85. Renison DM, Forouhar FA, Levine JB, Breiter JR. Filiform polyposis of the colon presenting as massive haemorrhage. An uncommon complication of Crohn's disease. *Am J Gastroenterol* 1983; **78**: 413–16.
86. Mesleh G, Lemons J. Massive gastrointestinal haemorrhage in Crohn's disease. *IMJ* 1983; **164**: 182–5.
87. Korelitz BT, Janowitz HD. Ulcerative colitis—general considerations. In: Turell R, ed. *Diseases of the Colon and Anorectum.* WB Saunders, Philadelphia, Vol 2; chapter 33: page 639.
88. Sutton R, Blake JRS. Massive rectal bleeding following faecal impaction. *Br J Surg* 1984; **71**: 631.
89. Turell R. Laceration to anorectum—incident to enema. *Arch Surg* 1960; **81**: 953–4.
90. Karawada Y, Brady L, Maysumoto T. Radiation injury to the large and small intestines *Am J Protocol* 1974; **25**: 49–53.
91. Taverner D, Talbot IC, Carr-Locke DL, Wicks ACB. Massive bleeding from the ileum: a late complication of pelvic radiotherapy. *Am J Gastroenterol* 1982; **77**: 29–31.
92. Wilson SE, Stone RT, Christie JP, Passaro E. Massive lower gastrointestinal bleeding from intestinal varices. *Arch Surg* 1979; **114**: 1158–61.
93 Foutch PG, Sivak MV, Sivak V. Colonic variceal haemorrhage after endoscopic injection sclerosis of oesophageal varices. *Am J Gastroenterol* 1984; **79**. 756–60.
94. Waxman JS, Tarkin N, Dave P, Waxman M. Fatal haemorrhage from rectal varices. *Dis Colon Rect* 1984; **27**. 749–50.
95. Gould PC, Khawaja FI, Rosenthal WS. Antibiotic associated haemorrhagic colitis. *Am J Gastroenterol* 1982; **77**: 491–3.
96. Haycock CE, Suryanarayan G, Spiller CR, Lazaro EJ. Massive haemorrhage from benign solitary ulcer of the rectum. *Am J Gastroenterol* 1983; **78**. 83–5.
97. Chaussade S, Desechalliers JP, Lerebours E *et al.* Gastrointestinal bleeding in patients with anticoagulant therapy—a retrospective study of 178 consecutive cases. *Gastroenterol Clin Biol* 1984; **8**: 152–6.
98 Barbier P, Luder P, Triller J *et al.* Colonic haemorrhage from a solitary minute ulcer. *Gastroenterology* 1985; **88**: 1065–8.
99 Reilly LM, Ehrenfeld WK, Goldstone J, Stoney RJ. Gastrointestinal tract involvement by prosthetic graft infection: the significance of gastrointestinal haemorrhage *Ann Surg* 1985; **202**: 342–7.

Paper accepted 15 April 1988

P, 25, 330.

Br. J. Surg. 1988, Vol. 75, July, 641–644

Growth rate of hepatic metastases in colorectal carcinoma

I. G. Finlay, D. Meek*, F. Brunton† and C. S. McArdle

*University Department of Surgery and *Department of Radiology, Royal Infirmary, Glasgow, and †Department of Physics, Western Infirmary, Glasgow, UK*

Correspondence to: Mr I. G Finlay

The rates of growth of 29 hepatic metastases from 15 patients with primary colorectal carcinoma were studied using serial computed tomography (CT). Eleven metastases were found by the surgeon at laparotomy (overt metastases); the remaining eighteen were not evident to the surgeon at laparotomy, but were detected by CT scan during the immediate postoperative period (occult metastases). An estimate of tumour volume doubling time was obtained from a semi-logarithmic plot of tumour cell number against time. The mean doubling time for the overt metastases was 155 ± 34 days ($\pm$s.e.m.) compared with 86 ± 12 days ($P<0{\cdot}05$) for the occult metastases. The age of the metastases at the time of surgery was estimated by extrapolation of the observed growth curve assuming Gompertzian kinetics. The mean age of the overt metastases was $3{\cdot}7 \pm 0{\cdot}9$ years ($\pm$s.e.m.) The corresponding age of the occult metastases was $2{\cdot}3 \pm 0{\cdot}4$ years.

Keywords: Growth kinetics, hepatic metastases, colorectal carcinoma

There have been comparatively few opportunities to study growth rates of human tumours. Early studies used direct measurement of recurrent nodules in mastectomy wounds as a model for assessing tumour growth[1,2]. Estimation of the growth rate of human visceral tumours has predominantly depended on serial chest radiographs in patients with pulmonary metastases[3,4]. These studies of relatively large tumour deposits, late in the natural history of the disease, have assumed exponential growth between observations.

Tumour growth is a complex phenomenon with many variables. The growth rate at any time is dependent on the proportion of cells actively dividing; promoting or inhibitory factors; available nutrients; mean cell cycle time; and degree of cell death[5].

Even less information is available regarding the early growth phase of human tumours because of ethical considerations. It has been demonstrated in animal tumours that there is slowing of the growth rate with increasing tumour size[6,7]. The initial growth in these experimental tumours is exponential, but as the size increases the growth rate continually decreases. This pattern of growth has been described mathematically by the Gompertz equation[8,9]. If a similar growth pattern applied to colorectal carcinoma then this would have important implications for our understanding of the natural history of the disease.

In the present study we have employed serial hepatic computed tomography (CT) scanning in the measurement of growth of hepatic metastases from colorectal carcinoma.

Patients and methods

Fifteen patients undergoing surgery for histologically proven colorectal carcinoma were studied Of these, five patients had overt hepatic metastases detected by the surgeon at the time of laparotomy. The remaining ten patients had an apparently disease-free liver on routine palpation at surgery. Hepatic CT performed during the immediate postoperative period demonstrated the presence of hepatic metastases (occult metastases) in those ten patients

Serial CT scans were obtained in all 15 patients using an EMI 5005 Whole Body Scanner with a 13 mm collimated beam, a 32 cm field size and a 320 × 320 reconstruction matrix Scans were performed at 15 mm intervals. Progressive enlargement of the hepatic metastases was demonstrated on serial CT scanning performed on at least 2 further occasions within 1 year of surgery in all 15 patients A strict protocol was maintained for follow-up and scanning patients with occult metastases and has been described before[21]. For ethical reasons those patients with overt metastases were scanned at their convenience All patients died primarily from hepatic disease within 3 years In keeping with routine practice at that time no therapy was given during the period of observation and serial scanning.

Metastatic deposits were included in the growing study if. (a) the margins were clearly identified on serial scanning; (b) the metastases remained single and did not become contiguous; (c) the metastases did not lie immediately adjacent to the capsule of the liver (since these features may influence growth) For these reasons, although 39 metastases were identified at the time of initial surgery, only 29 were studied. Eleven of these hepatic metastases were overt and eighteen were 'occult' (one metastatic deposit studied in five patients, two in eight patients, three in one patient and five metastases in one patient).

The volume of each metastasis was calculated from the maximum and minimum cross sectional diameter of the CT slices using the following formula.

$$V=\frac{\pi}{6}ab\frac{ab}{2} \qquad V=\text{volume}$$

(a and b are the maximum and minimum cross-sectional diameters). Tumour cell number was calculated from the volume assuming 10^9 cells per cm^3. For each metastasis an estimate of the instantaneous tumour volume doubling time (doubling time during the period of observation with serial CT) was obtained from a semi-logarithmic plot of tumour cell number against time Comparison of the mean tumour doubling time and tumour cell number between overt and occult hepatic metastases was undertaken using a Mann–Whitney U test.

The age of each metastasis at the time of surgery was estimated by mathematical extrapolation of the observed growth curves to an assumed one cell origin. Separate calculations were made assuming both exponential and Gompertzian growth kinetics[8].

Results

The observed rates of growth for the overt and occult hepatic metastases (logarithmic data) are shown in *Figures 1* and *2* respectively. The mean instantaneous tumour volume doubling time for the overt metastases was 155 ± 34 days ($\pm$s.e.m) compared with 86 ± 12 days for the occult metastases (*Tables 1* and *2*, $P<0{\cdot}05$). As the tumours increased in size the growth rate decreased (*Figure 3*, correlation coefficient 90·54 $P<0{\cdot}02$).

The mean tumour cell number at the time of the first scan for overt metastases was $25{\cdot}2 \pm 1{\cdot}2 \times 10^9$ ($\pm$s.e.m.). The corresponding mean cell number for occult metastases was $9{\cdot}7 \pm 0{\cdot}5 \times 10^9$. Small metastases were noted to be initially elliptical, becoming spherical at a diameter of approximately 1·5 cm

The mean survival time of the five patients with overt hepatic metastases, from the time of the first scan, was 10 ± 1·4 months (± s.e.m.). The corresponding survival for those patients with occult hepatic metastases was 17 ± 1·8 months (± s.e.m.).

The estimated age of each metastatic deposit, assuming a one cell origin and both exponential and Gompertzian growth, is given in *Tables 1* and *2*. The mean age of the overt metastases assuming exponential growth was 14 ± 3·0 years (± s.e.m.): the corresponding age assuming Gompertzian growth was 3·7 ± 0·9 years. The mean age of the occult hepatic metastases assuming exponential growth was 7·5 ± 1·0 years (± s.e.m.). The corresponding age assuming Gompertzian growth was 2·3 ± 0·4 years.

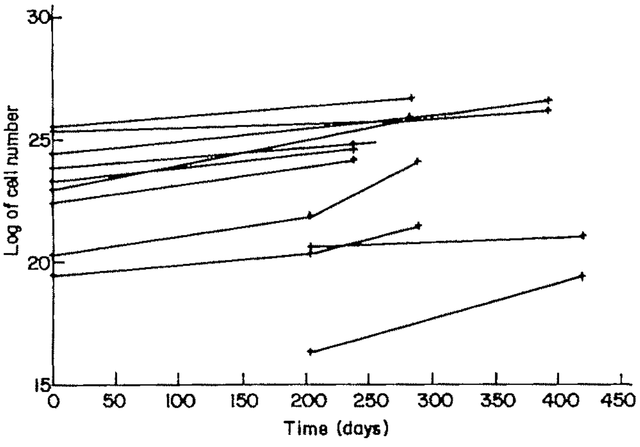


Figure 1 *Growth of overt hepatic metastases during the observed phase following identification by computed tomography at the time of surgery*

Discussion

Although colorectal carcinoma is the second most frequent cause of death from malignant disease and metastasizes predominantly to liver, there have been no reports of the growth rate of hepatic metastases from the disease. The present study was facilitated by the ability of CT to provide a three-dimensional image allowing volume measurements of hepatic metastases at a relatively early stage in tumour growth. The mean instantaneous tumour volume doubling times for the overt and occult hepatic metastases were 155 and 86 days respectively. Interestingly, the rate of tumour growth decreased as the tumour volume increased when analysis was undertaken for all the metastases studied. The numbers were insufficient to evaluate overt and occult metastases separately.

Although the growth rate of hepatic metastases from colorectal carcinoma has not previously been reported, studies have been undertaken of growth rates of pulmonary metastases. Using serial chest radiographs, Collins reported a median

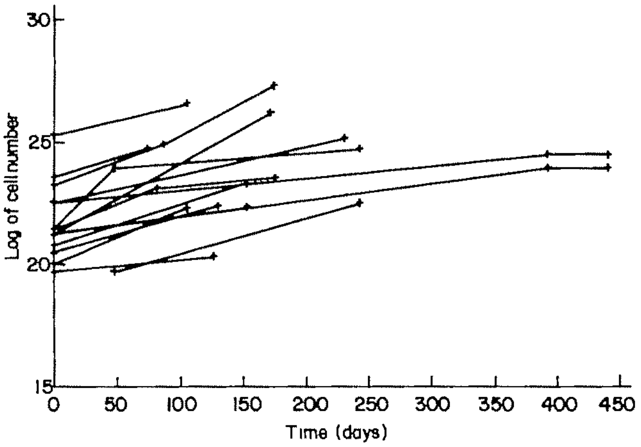


Figure 2 *Growth of occult hepatic metastases during the observed phase following identification by computed tomography at the time of surgery. Growth of four metastases excluded to simplify the graph*

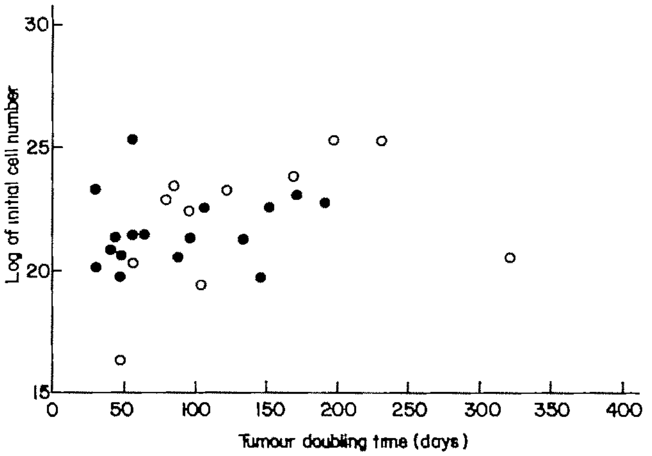


Figure 3 *Comparison of tumour volume doubling time with the log tumour cell number at the first observation.* ○, *Represents overt hepatic metastases;* ●, *represents occult hepatic metastases*

Table 1 *Doubling times and predicted age of overt hepatic metastases assuming exponential and Gompertzian growth*

Patient	No. of serial scans used	Instantaneous tumour doubling times	Tumour cell no. at first scan	Predicted age of metastases at first scan assuming exponential growth (years)	Predicted age of metastases at first scan assuming Gompertzian growth (years)
1	2	94	$5{\cdot}5\times10^{9}$	8·3	2·6
	2	122	$1{\cdot}3\times10^{10}$	15·9	4·2
	2	169	$2{\cdot}3\times10^{10}$	11·2	3·1
2	3	57	$6{\cdot}5\times10^{8}$	4·5	1·5
	3	104	$2{\cdot}7\times10^{8}$	7·9	3·5
3	2	85	$1{\cdot}5\times10^{10}$	8·2	1·3
	2	397	$1{\cdot}1\times10^{11}$	39·9	7·2
4	3	80	$9{\cdot}0\times10^{9}$	7·3	1·3
	3	231	$1{\cdot}0\times10^{11}$	23·0	3·4
5	2	48	$1{\cdot}2\times10^{7}$	2·8	1·3
	2	321	$8{\cdot}8\times10^{8}$	25·8	11·4

Table 2 *Doubling times and predicted age of occult hepatic metastases assuming exponential and Gompertzian growth*

Patient	No. of serial scans used	Instantaneous tumour doubling times	Tumour cell no. at first scan	Predicted age of metastases at first scan assuming exponential growth (years)	Predicted age of metastases at first scan assuming Gompertzian growth (years)
1	3	30	$1·3 \times 10^{10}$	2·7	0·4
	3	57	$2·0 \times 10^{9}$	4·9	1·6
2	3	64	$2·1 \times 10^{9}$	5·5	1·9
	2	48	$3·8 \times 10^{8}$	3·7	1·5
3	2	107	$6·3 \times 10^{9}$	10	2·5
4	2	44	$1·8 \times 10^{10}$	4·1	1·1
5	2	31	$5·2 \times 10^{8}$	5·6	0·8
	2	56	$9·8 \times 10^{10}$	2·5	1·0
6	2	89	$8·8 \times 10^{8}$	7·1	2·3
	2	135	$1·8 \times 10^{9}$	11·2	3·8
	2	153	$6·4 \times 10^{9}$	13·5	3·8
	2	172	$1·1 \times 10^{10}$	15·6	4·1
	2	192	$8·2 \times 10^{9}$	17·5	5·0
7	2	140	$3·8 \times 10^{8}$	11·4	5·4
8	2	45	$1·8 \times 10^{9}$	4·2	0·8
9	2	49	$8·8 \times 10^{8}$	4·0	1·6
10	2	42	$1·1 \times 10^{9}$	3·5	1·2
	2	97	$1·8 \times 10^{9}$	8·2	3·2

doubling time for pulmonary metastases of 116 days (range 34–210)[10], while Spratt and Spratt using a similar technique found a mean doubling time of 109 days[3]. As in the present study, those authors demonstrated large variations in doubling times between metastases. CT has recently been used by Havelaar *et al.* to study growth of intra-abdominal recurrent disease from colorectal carcinoma in four patients[11]. These patients correspond to the occult group in the present study having tumour volume doubling times of between 50 and 95 days.

In addition, there have been four studies reporting the growth rate of primary colorectal tumours. These arose from opportunistic situations when serial barium enemas were performed but no treatment was instituted[12–15]. The most recent, by Bolin *et al.*, reported a mean doubling time for primary tumours of 130 days[15]. They suggested that previous studies reporting longer tumour doubling times for primary colorectal carcinoma of approximately 600 days were erroneous as they included slow-growing adenomata. In view of the observer error in these types of study the doubling times for primary tumours, pulmonary and now hepatic metastases from colorectal carcinoma are remarkably similar. An explanation for this has been offered by Collins[10]. He suggested that a single volume doubling of a large tumour leads to a relatively large increment in diameter which accommodates any observer error.

It is of interest that hepatic metastases in the present study were noted to be initially elliptical in shape, becoming spherical at approximately 1–1·5 cm in diameter. A probable explanation for this observation is that tumours grow in an elliptical fashion as they follow blood vessels, thereby gaining an excellent supply of nutrient which allows exponential growth. As they expand, becoming spherical, nutrient is reduced with a corresponding reduction in growth rate.

Attempts have been made to extrapolate mathematically from the observed phase of growth to calculate the approximate age of metastases at the time of the first clinical or radiological detection of the metastatic deposit[1–4]. These calculations have been based on the assumption that tumours arise from a single cell origin and that the growth kinetics are exponential. In addition, it is assumed that the tumour only contains cells without stroma. It was noted, however, that tumour growth is complex with many variables[5]. Further, it is probable that human tumours exhibit inhibition or slowing of growth rate with increasing size similar to that observed in animal models. Indeed a differential growth pattern of this type has been suggested for human multiple myeloma[16] and for metastases from testicular primary tumours[17]. The observation in the present study that instantaneous tumour volume doubling times increase with increasing tumour size supports this principle for colorectal carcinoma.

A simple extrapolation of growth curves to indicate the age of metastases is a precarious exercise. Nevertheless, the procedure has been undertaken using the data obtained in the present study and assuming both exponential and Gompertzian growth patterns. There is a large discrepancy and apparent paradox in the predicted age of the metastases at the time of surgery, dependent on which method is employed. Although exponential growth is the faster theoretical rate, the age of the metastases calculated on this basis is apparently older. This happens because the observation period occurs late in the natural history of the disease: perhaps at the 20–24th doubling of the tumour. It has been estimated that the average tumour will undergo only 26–30 doublings in its lifespan. Since at this stage tumour growth is slow, then the doubling time is long. Exponential extrapolation based on these long doubling times will lead to an older predicted age of the tumour. The same calculation based on Gompertzian growth compensates for these prolonged doubling times by assuming faster growth rates at a smaller diameter.

Based on Gompertzian growth, the mean age of the overt and occult metastases at the time of surgery was calculated to be 3·7 and 2·3 years respectively. There is, however, wide variation in doubling time between metastases in the same patient and also between patients. This feature has been observed before[1–4]. There are several possible explanations for this finding. Firstly, metastases may not arise as a single cell, but from clumps of cells of varying size. Secondly, the metastatic process is probably a continuing one which leads to metastases of different age with different growth rates. Thirdly, large tumour deposits would appear to virtually stop growing.

The mean survival time of the patients with overt and occult metastases from the time of surgery was 10 and 17 months respectively. On the basis of these results, the overall mean lifespan of overt and occult hepatic metastases was 52 and 47 months respectively. Although we would wish these to be considered only approximate values, it is of interest that the lifespan should be similar given that these figures were independently calculated.

It is known that, despite apparently curative resection of the primary tumour, 40–50 per cent of patients with colorectal carcinoma die predominantly from disseminated disease within 5 years[18,19]. The disappointing results obtained using current modes of treatment for disseminated disease have led clinicians to believe that the primary tumour must be detected earlier in an attempt to pre-empt the metastatic process. In Nottingham, for example, it was observed that the average time interval between the onset of symptoms and surgical excision of the primary tumour for patients with rectal carcinoma was 9 months[20]. The apparently laudable conclusion of that study was that a reduction in the period of delay during which patients are symptomatic may improve outcome. Several recent studies have demonstrated that up to 30 per cent of patients undergoing apparently curative surgery already have hepatic metastases which are not evident to the surgeon at the time of laparotomy (occult hepatic metastases)[21–23]. These occult deposits have been detected using carefully employed CT[21], dynamic scintigraphy[22] and intra-operative ultrasound[23]. Perhaps of more importance, with regard to our understanding of the natural history of colorectal cancer, was the observation in these studies that very few patients who did not have occult metastases demonstrated at the time of surgery subsequently developed disseminated disease at follow-up. This suggests that most patients destined to develop disseminated disease have already done so at the time of laparotomy.

The results of the present study further suggest that even these 'occult' metastases may have been present for as long as a mean of 2·3 years before the time of surgery. On this basis, it would appear unlikely that reducing the time interval during which patients are symptomatic will lead to a substantial reduction in the number of primary tumours which have already metastasized to the liver. Clearly, primary tumours must be detected at least at an asymptomatic stage and it remains to be seen whether even this will allow us to pre-empt the metastatic process.

References

1. Philippe E, Gal Le Y. Growth of seventy-eight recurrent mammary cancers. *Cancer* 1968; **21**. 461–7.
2. Lee YN, Spratt JS. Rate of growth of soft tissue metastases of breast cancer *Cancer* 1972, **29**. 344–6
3. Spratt JS, Spratt TL. Rates of growth of pulmonary metastases and host survival. *Ann Surg* 1964; **159**: 161–71.
4. Lokich J, D'Orsi C, Smith E *et al.* Tumour growth and regression rates relative to tumour size. *Cancer* 1981, **47**: 1415–20.
5. Baserga R. The cell cycle. *New England J Med* 1981, **304**: 453–9.
6. Laird AK. Dynamics of tumour growth. *Br J Cancer* 1964; **18**: 490–502.
7. Simpson-Herren L, Lloyd HH Kinetic parameters and growth curves for experimental systems. *Cancer Chemother Rep* 1970; **54**: 143–74.
8. Gompertz B. On the nature of the function expressive of the law of human mortality and on a new mode of determining the value of life contingencies. *Philos Trans R Soc, London* 1825; **115**: 513–85.
9. Norton L, Simon R, Brereton HD *et al.* Predicting the course of Gompertzian growth *Nature* 1976; **264**: 542–4
10. Collins VP. Time of occurrence of pulmonary metastases from cancer of colon and rectum. *Cancer* 1962; **15**: 387–95.
11. Havelaar IJ, Sugarbaker PH, Verness M *et al.* Rate of growth of intra-abdominal metastases from colorectal cancer *J Exp Clin Cancer Res* 1983, **2**. 55–6
12. Welin S, Youker J, Spratt JS. The rate and patterns of growth of 375 tumours of the large intestine and rectum. *AJR* 1963, **90**: 673–87.
13. Ekelund G, Lindstrom C, Tosengron JE. Appearance and growth of early carcinoma of the colon-rectum. *Acta Radiol* (*Diagn*) *Stockh* 1974; **15**: 670–9.
14. Gigiel LS, Figiel SJ, Wieterson FK. Roentgenologic observations of growth rates of colonic polyps and carcinoma. *Acta Radiol* (*Diagn*) (*Stockh*) 1963; **3**: 417–29.
15. Bolin S, Nilsson E, Sjodhal R. Carcinoma of the colon and rectum—growth rate. *Ann Surg* 1983, **198**: 151–8.
16. Sullivan PW, Salmon SE. Kinetics of tumour growth and regression in IgG multiple myeloma. *J Clin Invest* 1972; **51**: 1697–708.
17. Demicheli R. Growth of testicular neoplasm lung metastases: tumour specific relation between two Gompertzian parameters. *Eur J Cancer* 1980; **16**: 1603–8
18. Gill PE, Morris PJ. The survival of patients with colorectal cancer treated in a regional hospital *Br J Surg* 1978; **65**: 17–20.
19. Lockhart-Mummery HE, Ritchie JK, Hawley PR The results of surgical treatment for carcinoma of the rectum at St. Mark's Hospital from 1948–72. *Br J Surg* 1976; **63**: 673–7.
20. Holliday HW, Hardcastle JD. Delay in diagnosis and treatment of symptomatic colorectal cancer. *Lancet* 1979; i: 309–11.
21. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. *Br J Surg* 1986; **73**: 732–5.
22. Leveson SH, Wiggins PA, Giles GR, Parkin A, Robinson PJ Deranged liver blood flow patterns in the detection of liver metastases. *Br J Surg* 1985; **72**: 128–30.
23. Machi J, Isomoto H, Kurohiji T *et al.* Detection of unrecognized liver metastases from colorectal cancers by routine use of operative ultrasonography *Dis Colon Rectum* 1986, **29**: 405–9.

Paper accepted 17 February 1988

Br. J. Surg. 1988, Vol. 75, July,
645–647

Operative mortality rate and surgery for colorectal cancer

S. C. W. Brown,
S. Walsh and P. A. Sykes

Department of Surgery,
Park Hospital, Davyhulme,
Manchester M31 3SL, UK
Correspondence to. Mr P. A Sykes

Different authors use different definitions of operative mortality rate when reporting results of their operations. Four definitions used in current literature were applied to our own series of 578 patients with colorectal carcinoma. The operative mortality rate was found to vary from 7·3 per cent to 12·2 per cent, depending on the definition used. 'Death within 30 days of the last operation' was the definition which best reflected true operative deaths. We urge that this definition of operative mortality rate be adopted as a standard for all operations.

Keywords: Colorectal carcinoma, operative mortality rate, definition

Colorectal cancer is the second most common cause of cancer death in the United Kingdom, accounting for over 15 000 deaths per year[1]. Some of these deaths are directly attributable to the major surgery involved in treating the disease. Many factors, such as age and the clinical stage of the disease, contribute to the observed variation in operative mortality rate figures, 2·1–17 per cent[2,3], but comparison between series is made more difficult by the absence of a uniform definition of an 'operative death'.

It is known that comparison of survival figures between recorded series is hampered by the use of different definitions of survival[4]. For example, a 3-year survival rate of 36 per cent became 43 per cent when only patients treated surgically were considered, and 47 per cent if patients were included who, although alive at 3 years, were known to have recurrence of symptoms.

The aim of the present study is to examine the definitions of 'operative death' currently used in the literature, to discover how the mortality rate figure is affected if different definitions are applied to a series of colorectal cancer patients, to examine the actual cause of death for the patients encompassed by each definition, and to promote discussion which will result in a single definition being uniformly adopted.

Methods and results

Data have been collected prospectively on 578 patients treated for colorectal cancer between 1981 and 1985 by the 12 surgeons of the North-West of England Gastro-intestinal Tumour Group. Of these patients, 550 underwent surgery, making an operability rate of 95·2 per cent; 492 (85·1 per cent) resections were performed and, of these, 339 (58·6 per cent) were considered to be 'curative', a term used to denote resections which had included excision of all visible tumour.

A review of the literature shows that four definitions of operative mortality are in current use (*Table 1*), namely: I, death within 30 days of operation[2,3,5–7]; II, death within 60 days of operation[8]; III, death within 90 days of operation[9]; IV, death while still undergoing treatment as an in-patient[10,11]. The number of deaths and the overall operative mortality for each definition when applied to our series is shown in *Table 2*. The rate rises from 7·4 per cent (41 patients) if the definition is taken as death within 1 month of surgery, to 10·0 per cent (55 patients) if 2 months, and to 12·2 per cent (67 patients) if the definition is taken as 3 months. Forty patients died while still in hospital, but one of these deaths was 127 days after surgery; forty-one patients (7·4 per cent) died within a month of surgery and forty (7·3 per cent) died while still in hospital. Although these figures are similar, only 33 patients were common to both groups. The interval from the last operation to death, and the number of deaths that occurred while patients were still undergoing in-patient treatment, are shown in *Figure 1*.

Death may be due to cardiorespiratory complications,

Table 2 *Operative mortality in 550 patients according to definition used*

Definition	No. of deaths	Operative mortality rate (%)
I	41	7·4
II	55	10·0
III	67	12·2
IV	40	7·3

Table 1 *Operative mortality rates for colorectal cancer according to the definition used*

Definition	Study (first author)	Operative site	Dates	Operative mortality rate (%)
I: Death within 1 month of surgery	Clarke[3]	Colon and rectum	1968–69	17·0
	Turunen[5]	Colon and rectum	1966–75	6·5
	Habib[6]	Colon and rectum	1972–77	8·7
	Bear[7]	Colon and rectum	1976–79	13.0
	Lockhart-Mummery[2]	Rectum only	1948–52	7·0
II. Death within 2 months of surgery	Hughes[8]	Rectum only	1951–78	6·7
III: Death within 3 months of surgery	McDermott[9]	Colon and rectum	1950–78	7·0
IV. Death while still undergoing in-patient treatment	Whittaker[11]	Rectum only	1955–68	10·6
			1968–72	2·1
	Umpleby[10]	Colon and rectum	1969–75	17·0
Not given	Lea[12]	Colon and rectum	1969–78	5·4
	Evans[13]	Colon only	1967–76	17·0

0007-1323/88/070645-03$3 00 © 1988 Butterworth & Co (Publishers) Ltd

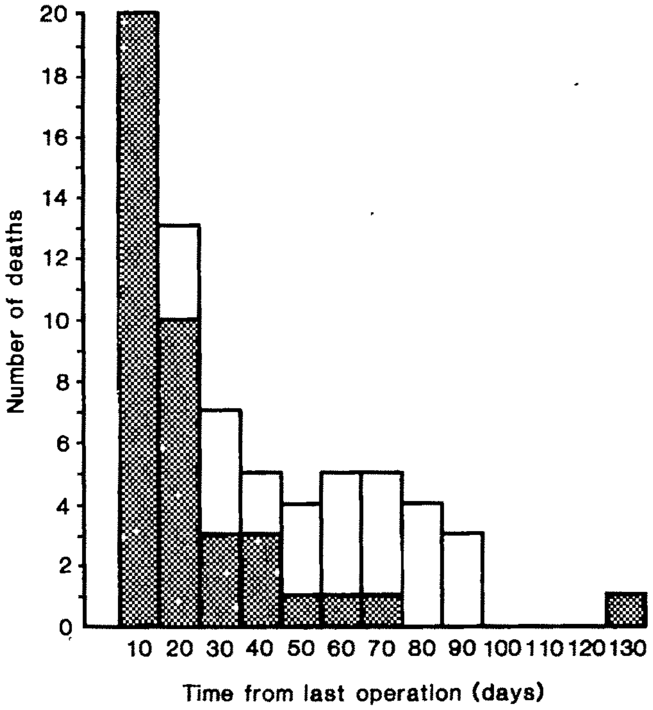


Figure 1 *Time interval between surgery and death for patients still undergoing in-patient treatment and those discharged from hospital.* ▨, *Death while still an in-patient,* ☐, *death occurring after first discharge from hospital*

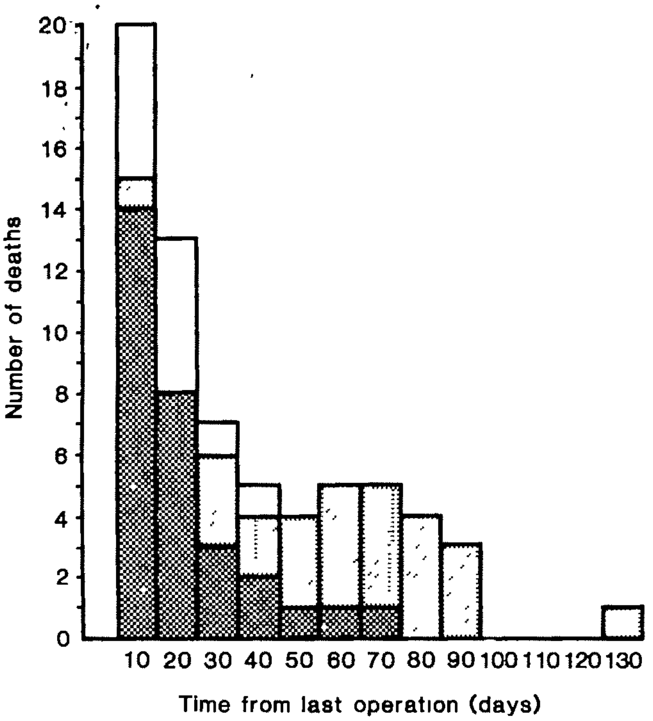


Figure 2 *Time interval between surgery and death, indicating cause of death* ▨, *Cardiorespiratory,* ■, *cancer,* ☐, *surgical*

disseminated malignant disease, or surgical causes (i.e. death attributable directly to surgical technique, such as sepsis due to anastomotic breakdown or haemorrhage). *Figure 2* shows the timing of the deaths for each of these three categories. Cardiorespiratory complications are the commonest cause, and occur in greatest number in the first three postoperative weeks. Deaths from the progression of malignant disease increase with the number of days from surgery Deaths from surgical complications are confined to the first month. Two deaths attributed to 'sepsis' occurred on the first postoperative day, in patients presenting as emergencies with peritonitis.

Table 3 *The cause of death as a percentage of the total number of deaths for each definition group*

	Causes of death					
	Surgical		Cardiorespiratory		'Cancer'	
Definition	No	%	No.	%	No.	%
I	11	27	26	63	4	10
II	12	22	29	54	13	24
III	12	18	30	46	24	36
IV	11	28	24	60	5	13

The cause of death as a percentage of the total operative death for each definition group is shown in *Table 3*. Deaths from cancer rise from 9·8 per cent to 35·8 per cent if definition III is used instead of definition I.

Discussion

From the variation in operative mortality rate observed in our series, it is clear that the different definitions used in the current literature add substantially to the difficulties of making direct comparisons between series. Furthermore, different causes of death are caught by the different definitions. An ideal definition of operative mortality should include only those deaths that occur as a result of an operation being performed, and deaths from advanced malignancy should therefore be excluded. Some deaths from cardiorespiratory causes may be attributable in part to the surgery and should be included, especially as some may be preventable.

A definition specifying a fixed time interval from operation to death has the advantage of facilitating direct comparison between series. We suggest this interval be 30 days. In our series this included all deaths we considered to be due to surgical complications with the exception of one, which occurred on the 36th day. The majority of deaths from cardiorespiratory complications took place in the first 30 days (84 per cent), and it is perhaps reasonable to assume that a cardiorespiratory event is not directly related to the operation after 30 days have elapsed. Even this definition will include some deaths which were due to disseminated carcinoma (4 of 550 patients in our series). These cases can be excluded if this definition of operative mortality rate is applied only to patients who have undergone 'curative' resections.

We recommend that death within 30 days of surgery be the definition of choice for operative mortality rate. Careful analysis of patient selection in different series must be carried out if meaningful comparisons are to be made. However, adoption of a standard definition must surely be the first and perhaps most important step towards this aim.

Acknowledgements

The patients in this study were admitted under the care of the following consultants (members of the North-West of England Gastro-intestinal Tumour Group): Mr J. Bancewicz (Salford); Mr J. Duthie (Oldham); Mr B D. Hancock (Wythenshawe); Mr E M. Hoare (Trafford); Professor M. Irving (Salford); Mr R. D. Kingston (Trafford), Mr I. MacLennan (Manchester), Mr N. K. Maybury (Wigan); Mr W Orr (Manchester), Mr P. F. Schofield (Manchester); Mr P A. Sykes (Trafford); Mr D. E F. Tweedle (Manchester).

References

1 Mortality Statistics, 1983. Office of Population Censuses and Surveys for England and Wales.

2 Lockhart-Mummery HE, Ritchie JK, Hawley PR. The results of surgical treatment for carcinoma of the rectum at St. Mark's Hospital from 1948 to 1972. *Br J Surg* 1976; **63**. 673–7

3. Clarke DN, Jones PF, Needham CD. Outcome in colorectal carcinoma; seven-year study of a population. *Br Med J* 1980; **280**: 431–5.
4. Schofield PF, Walsh S, Tweedle DEF. Survival after treatment of carcinoma of the rectum *Br Med J* 1986; **293**; 496–7.
5. Turunen MJ, Peltokallio P. Surgical results in 657 patients with colo-rectal cancer. *Dis Colon Rectum* 1983; **26**: 606–12.
6. Habib NA, Peck MA, Sawyer CN, Blaxland JW, Luck RJ. An analysis of the outcome of 301 malignant colo-rectal tumours. *Dis Colon Rectum* 1983; **26**: 601–5.
7. Bear HD, MacIntyre J, Burns HJG, Jarrett F, Wilson RE. Colon and rectal carcinoma in the West of Scotland. *Am J Surg* 1984; **147**: 441–6.
8. Hughes ESR, McDermott FT, Masterton JP, Cunningham IGE, Polglase AL. Operative mortality following excision of the rectum. *Br J Surg* 1980; **67**: 49–51.
9. McDermott FT, Hughes ESR, Pihl E, Milne BJ, Price AB. Comparative results of surgical management of single carcinomas of the colon and rectum; a series of 1939 patients managed by one surgeon. *Br J Surg* 1981; **68**: 850–5.
10. Umpleby HC, Bristol JB, Rainey JB, Williamson RCN. Survival of 727 patients with single carcinoma of the large bowel. *Dis Colon Rectum* 1984; **27**: 803–10.
11. Whittaker M, Goligher JC. The prognosis after surgical treatment for carcinoma of the rectum. *Br J Surg* 1976; **63**: 384–8.
12. Lea JW, Covington K, McSwain B, Scott HW. Surgical experience with carcinoma of the colon and rectum. *Ann Surg* 1982; **195**: 600–7.
13. Evans JT, Vana J, Aronoff BL, Baker HW, Murphy GP. Management and survival of carcinoma of the colon: results of a national survey by the American College of Surgeons. *Ann Surg* 1978; **188**: 716–20.

Paper accepted 26 February 1988

Case report

Br. J. Surg. 1988, Vol. 75, July, 647–648

Penetrating arrow injuries

R. Visvanathan

The Departments of Surgery, The University Teaching Hospital and the General Hospital, Maiduguri, Nigeria

Correspondence to:
Dr R.Visvanathan, 91 Longwood Avenue, Suite 2,
Brookline, Massachusetts 02146, USA

That injuries caused by flighted arrows are unusual in modern surgical practice is reflected in the paucity of reported instances in the literature[1–4]. Such injuries are, however, not uncommon in certain tribal societies today and the five cases reported were collected over a 2-year period.

Patients and methods

Patient 1

A 27-year-old man with an arrow injury to the left side of his neck sustained approximately 4 h previously was admitted concious and in stable condition (*Figure 1a*). The left common carotid pulse was not felt. The right hand was limp with good elbow and shoulder movements. There was mild paresis of the right lower limb. At emergency surgery the arrow was found to have penetrated the left common carotid artery and lacerated the left jugular vein with the barbed arrowhead deeply embedded in the body of the first thoracic vertebra on its right anterolateral aspect. The overlying oesophagus was uninjured. The left common carotid artery and the left jugular vein were ligated and the arrowhead was removed (*Figure 1b*). The wound was closed with suction drainage. After surgical recovery, the hemiparesis improved on physiotherapy and the patient was able to walk unaided.

Patient 2

A 29-year-old man was admitted with the metal shaft of an arrow protruding through the fourth left posterior intercostal space between the medial scapular border and the spine (*Figure 2*). He had been injured 2 h previously and was dyspnoeic with a raised jugular venous pressure. An emergency left posterior thoracotomy revealed active bleeding from a laceration in the upper lobe of the lung. There was a tear in the pericardium adjacent to the atrioventricular border of the heart with approximately 40 ml of blood in the pericardial sac. The heart and the great vessels escaped injury. The arrow was removed and the pericardial sac was repaired around a suction drain. The pulmonary laceration was sutured and the chest closed with apical and basal water-seal drains. Recovery was uneventful on broad-spectrum antimicrobial therapy.

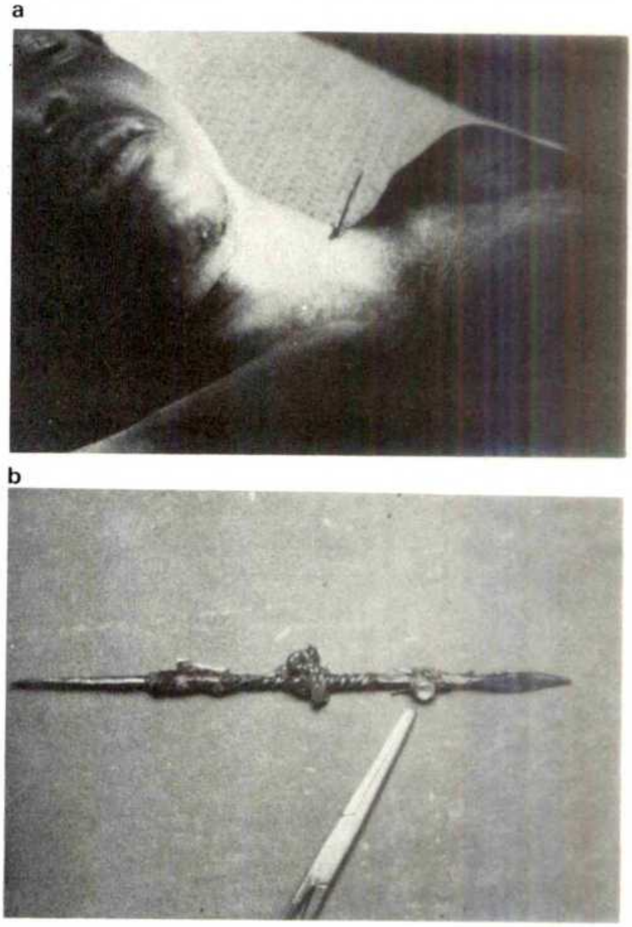


Figure 1 **a** *Patient 1 on presentation;* **b** *arrowhead removed from patient 1 with a segment of left common carotid artery impaled on it*

Patient 3

A 38-year-old man was seen following an arrow injury to his chest earlier that day. Attempts at extraction of the arrowhead had resulted in the shaft breaking off, leaving the arrowhead *in situ*. On examination there was an area of surgical emphysema in the lower anterolateral aspect of his left chest wall surrounding a puncture wound and the arrowhead was seen radiologically. The arrowhead was removed through a limited left thoracotomy and the pleural cavity drained. Recovery was uneventful on a postoperative course of antimicrobial agents.

0007–1323/88/070647–02$3.00 © 1988 Butterworth & Co (Publishers) Ltd

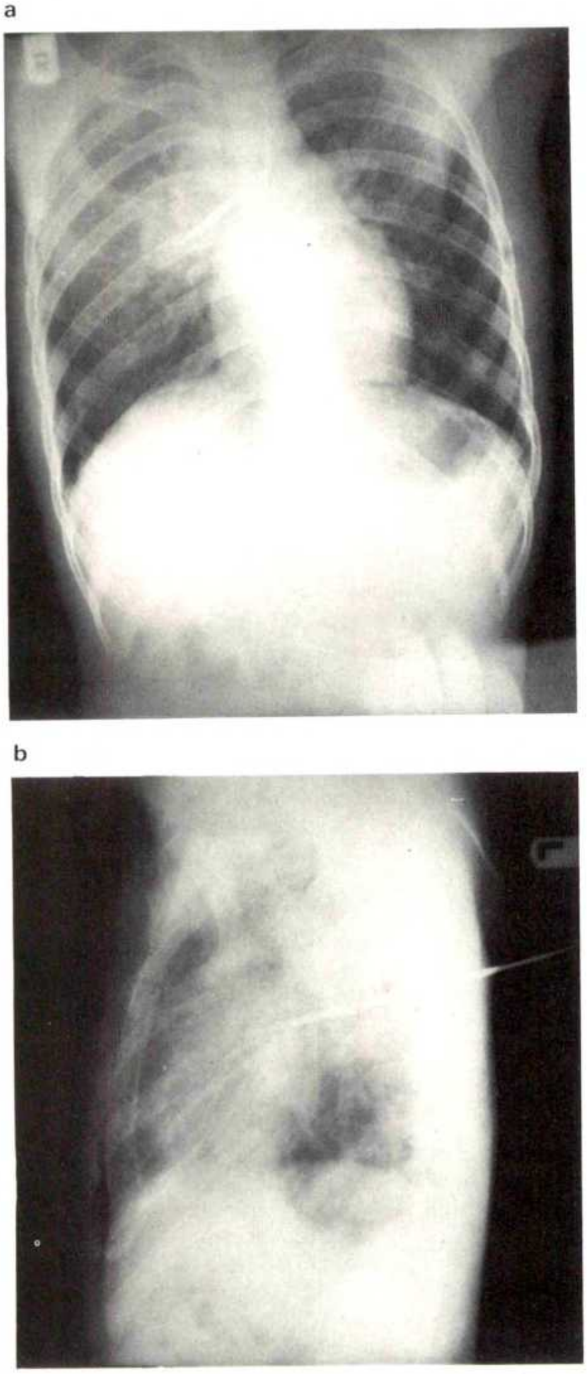


Figure 2 **a** *Anterior and* **b** *left lateral chest radiographs of patient 2*

Patient 4

A 21-year-old man was admitted as an emergency within 2 h of being shot in the abdomen with an arrow. His condition was stabilized and urethral catheterization produced faintly blood-stained urine. At laparotomy, bruised but viable loops of small bowel with tears in the mesentery were found, with a large retroperitoneal haematoma at the point of lodgement of the arrowhead lateral to the lumbar vertebrae. After removal of the missile and evacuation of the haematoma, the posterior wall was explored. The left ureter and the urinary bladder were found to be bruised but intact. The area was drained, the mesenteric lacerations sutured and the abdomen closed in layers. The patient recovered after a stormy postoperative course with a fluctuating temperature and a serosanguinous discharge lasting 12 days with delayed return of bowel function. Excretory urograms were normal.

Patient 5

A 19-year-old man was referred with a recent history of right-sided chest pain and breathlessness on exertion. He gave a history of an arrow injury to the right lower chest 2 months previously. The arrow had been removed intact and the wound healed without medical attention. A right-sided empyema thoracis was diagnosed on his visit and a basal chest drain produced 1650 ml of thick brownish pus. Decortication of the right lower lobe of the lung was performed electively with satisfactory lung expansion. Subsequent follow-up was normal.

Discussion

Victims of penetrating arrow injuries are generally stable on admission provided that no attempt is made to extract the missile before surgical exploration: such ill-advised attempts compound the injury and may precipitate massive bleeding. Plain radiography and selective angiography when vascular injury is suspected assist surgical exploration and repair. Post-surgical sepsis is inevitable unless meticulous attention is paid to wound toilet, débridement and drainage, with broad-spectrum antimicrobial therapy started early. Antitetanus immunization is advised after sensitivity testing on admission.

References

1. Singh RJ, Singh NK. Arrow injury. *J Indian Med Assoc* 1985; **83**: 65–6.
2. Saw EC, Arbegast NR, Comer TP. Crossbow arrow injury of the abdomen. *Arch Surg* 1973; **106**: 721.
3. Faber RG. Ureteric injury caused by penetrating arrow wound. *J R Coll Surg Edinb* 1974; **19**: 241–3.
4. Jeffrey KL, Bradley R. Thoracic and abdominal wound in a cat shot with an arrow. *Vet Med/Small Animal Clinician* 1981; **1**: 353–4.

Paper accepted 7 January 1988

Br. J. Surg. 1988, Vol. 75, July,
649–652

Clinicopathological assessment and staging of colorectal cancer

N. S. Williams, J. R. Jass and J. D. Hardcastle

*On behalf of the Staging Working Party set up by the Colorectal Sub-committee of the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR)**

Correspondence to:
Professor N. S. Williams, Surgical Unit, The London Hospital,
Whitechapel, London E1 1BB, UK

Compared with various common neoplasms, there is no national or international agreed clinicopathological staging system for colorectal cancer. Before such a system can be developed, however, there has to be agreement on the methods used for assessment. The Colorectal Sub-committee of the United Kingdom Co-ordinating Committee on Cancer Research has, through its working party on staging, agreed various recommendations as to how the clinical and pathological assessment of patients with colorectal cancer can be standardized. By applying these standardized criteria, patients undergoing surgery can be divided into those having curative *or* non-curative *operations, or operations which are* indeterminate for cure. *These recommendations represent the first step in ensuring uniformity in the classification of patients with colorectal cancer.*

Keywords: Colorectal cancer, assessment, staging

The need for a more uniform and relatively detailed clinicopathological assessment of patients with colorectal cancer is becoming increasingly obvious. Many of the adjuvant therapy trials, although not necessarily showing an overall benefit in survival, suggest that certain treatments are particularly useful in some subgroups of patients. Thus, the most recently completed MRC trial of pre-operative radiotherapy in rectal cancer[1] suggested a possible benefit for patients with fixed tumours, despite a relatively low dose of radiation. The portal perfusion of 5-fluorouracil (5FU) seems to enhance survival in patients with colonic tumours who do not have overt hepatic metastases[2]. Similarly, patients with rectal cancer may benefit by a combination of postoperative radiotherapy, 5FU and methyl CCNU according to a recent trial organized by the Gastrointestinal Tumour Study Group[3]. Comparisons between trials such as these are difficult because criteria and methods of assessment differ.

In order to select high risk groups suitable for a particular form of adjuvant therapy and to ensure that different groups of researchers are studying the same patients, it is important for them to have a common language. This approach has proved essential in the improved treatment of other neoplasms such as testicular tumours and the lymphomas which had previously proved resistant to treatment. The same approach should also be of benefit in the selection of patients for surgical manoeuvres. This is particularly relevant to patients with rectal cancer for whom a variety of sphincter-preserving techniques are now available.

The staging of colorectal cancer has until recently meant a classification based on the pathologist's examination of the excised specimen. The most well-known scheme has been that of Dukes[4,5], but other modifications of this scheme have become popular, particularly in the USA[6,7]. All of these systems subdivide carcinomas into the alphabetical divisions A, B and C. This nomenclature has at times led to confusion on both sides of the Atlantic since the different classifications vary in the criteria used to subdivide the groups. The TNM system was introduced[8] in order to standardize the pathological staging and make it more comprehensive. This system gives more information about the extent of direct and lymph node spread as well as taking into account the presence of metastases. Since its inception, the TNM system has not proved popular. Most surgeons and pathologists have tended to adhere to the simpler ABC systems, although some have added a 'D' category to signify the presence of metastases[9].

All of these classifications have been used to determine prognosis and, although there is an abundance of data which testify to their value in this regard, recent research has demonstrated their inadequacies. Thus, Finlay and McArdle[10] have demonstrated that a considerable proportion of patients thought to have an A, B or C lesion at the time of surgery, and believed by the surgeon to have undergone a curative resection, have occult hepatic metastases from which they subsequently die. These patients are 'D' cases from the beginning, but unfortunately the microscopic liver deposits cannot be detected at the time of operation, their presence only being proved by observation of their growth on serial imaging of the liver. Similarly, new insight into the mechanism of local recurrence has been provided by a meticulous study of microscopic disease in the pelvis after surgery for rectal carcinoma[11]. Other inadequacies of existing staging classifications relate to their failure to take account of local invasion of contiguous tissue and structures, a characteristic which in some studies overrides the prognostic significance of involved lymph nodes[12,13]. Although the presence of metastases is included in some staging classifications, the development of sophisticated imaging techniques has introduced the problem of differing diagnostic criteria in various units. Excepting distant spread, current classifications have taken no heed of clinical information. The recent Australian Clinicopathological Staging System[14] has to some extent attempted to rectify some of these inadequacies, but is open to criticism since assessment has not been standardized Before clinical factors can be included in a staging system, there has to be agreement on how assessment is performed, and the terms of reference have to be defined.

For the above reasons, the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) asked its colorectal sub-committee to set up a working party with the aim of standardizing the clinical and pathological assessment of colorectal cancer within the UK. This working party consisted of surgeons, pathologists, radiologists, radiotherapists and statisticians, each with particular expertise in the disease. The group was also joined by the Chairman of the Committee on Clinicopathology Staging of Large Bowel Cancer set up by the American Society of Colon and Rectal Surgeons, the aim being to achieve agreement on both sides of the Atlantic, with the ultimate hope of gaining an international consensus. The working party has met on several occasions, both as a whole and in small subgroups. It has considered the conventional and recently developed methods of assessing patients with colorectal carcinoma and determined which techniques are practical in most units and which should be studied in more detail. Below

---

* *A description of UKCCCR can be found in the Appendix*

0007-1323/88/070649-04$3 00

are listed the main practical recommendations reached by the working party. Further details will be available in a handbook published by the UKCCCR, obtainable from the Medical Research Council Head Office, 20 Park Crescent, London W1N 4AL, UK.

Recommendations

1 Pre-operative clinical assessment

(1.1–1.5 are applicable to rectal cancer only)

1.1 Palpation. This should be performed in the conscious state; and under anaesthetic only if it is deemed that an adequate examination is not possible with the patient awake.

1.2 The distance of the lower margin of the tumour from the anal verge. This should be determined using a rigid sigmoidoscope with the patient conscious and lying in the left lateral position.

1.3 Circumferential involvement. The number of quadrants of the bowel circumference which are involved should be indicated.

1.4 Fixity. Fixity on palpation should be classified as:
- (a) Fixed (to adjacent structures and immobile)
- (b) Tethered (extending through the wall and partially fixed)
- (c) Mobile (confined within the wall).

1.5 Assessment of local spread by scanning techniques. Whenever computerized tomography (CT) is available, it should be used to assess:
- (a) Degree of local spread
- (b) Distance of the tumour from the superior border of the anal sphincter
- (c) The presence of enlarged lymph nodes.

1.6 Histopathological grade of biopsy.
- (a) The biopsy should be stated as being adenocarcinoma or not.
- (b) The degree of differentiation should be classified as 'poor' or 'other'.

1.7 Detection of liver metastases.
- (a) The liver should be scanned in all patients with colorectal cancer.
- (b) Scanning should preferably be by CT, but ultrasound should be used if the latter is not feasible.
- (c) After scanning the liver should be classified as one of the following:
  - (i) Definite hepatic metastases present
  - (ii) Equivocal
  - (iii) Hepatic metastases not present.
- (d) Serum carcino-embryonic antigen (CEA) concentration should be determined if facilities are available. A high level (>50 ng/ml) suggests metastatic disease even if liver imaging is negative.

1.8 Assessment of established liver metastases.
- (a) The number of liver metastases should be expressed as 'solitary' or 'multiple'. If solitary, it should be stated if the metastasis is in the right or in the left lobe. If multiple, it should be stated if they are uni- or bilobar.
- (b) The percentage of liver involved on scanning should be quantified by the radiologist as:
  - (i) 0
  - (ii) $1<50$ per cent
  - (iii) $2>50$ per cent.

  If symptoms which are probably related to liver metastases are present, the symbol 'S' should be appended to each grade.

1.9 Exclusion of synchronous lesions. All patients with a colorectal carcinoma should have the remainder of the large bowel assessed preferably by colonoscopy before surgery, but if colonoscopy is not available or is technically impossible (e.g. a stenotic lesion is present), a double contrast barium enema should be performed.

(If pre-operative assessment cannot rule out synchronous lesions, these should be sought by:
- (a) Intra-operative palpation (see 2.1 below) supplemented, if facilities are deemed appropriate, by on-table colonoscopy, and/or
- (b) Postoperative colonoscopy.)

1.10 Assessment of the urological tract. A pre-operative intravenous urogram is not routinely required, but may be indicated in exceptional circumstances.

1.11 Assessment of lung fields. A routine chest X-ray should be obtained and the presence of any pulmonary metastases noted.

2 Intra-operative assessment

The surgeon should record the following details:

2.1 Presence of synchronous carcinomas or polyps.

2.2 Tumour site. If rectal, whether it is:
- (a) above or
- (b) below the peritoneal reflection.

2.3 Fixity of tumour
- (a) mobile
- (b) tethered
- (c) fixed.

If tethered or fixed the structure(s) to which the tumour is adherent should be specified. The surgeon must also specify if a biopsy has been taken from the area of invasion/adherence.

2.4 Tumour associated with local abscess/operative perforation.

2.5 Peritoneal metastases. If deemed to be present, a biopsy must be taken.

2.6 Enlargement of para-aortic lymph nodes. Biopsy should be taken.

2.7 Liver metastases. Site and number should be specified and biopsy taken.

2.8 Operative procedure. A statement about whether the operative procedure is:
- (a) curative or
- (b) palliative.

This must be made based on the surgeon's impression as to whether all macroscopic tumour has been removed or not. If there is any doubt on his part, he should state his uncertainty. If residual tumour is thought to remain, it should be biopsied.

2.9 Indication for operation. The indication for performing the operation should be stated.
- (a) elective or
- (b) emergency.

If emergency, the reason should be stated, e.g. perforation, obstruction, haemorrhage, other.

3 Pathological reporting

The pathologist should record the following characteristics:

3.1 Gross description.
- (a) Distance of upper edge of growth from proximal margin and lower edge of growth from distal margin (cm). State whether fixed or fresh.

(b) Axial and transverse diameters of growth (cm).
(c) Circumference of bowel at midpoint of tumour (cm).
(d) Appearance of tumour (protuberant, ulcerating, diffusely infiltrating).

3.2 Local spread.
(a) Spread through tissues of bowel wall:
  (i) Cannot be assessed (e.g. previous local excision or radiotherapy)
  (ii) Neoplastic process limited to mucosa. (This is often reported as severe dysplasia in UK)
  (iii) Limited to submucosa
  (iv) Limited to muscularis propria (externa)
  (v) Beyond muscularis propria but not penetrating peritoneum or invading adjacent organs
  (vi) Invades adjacent organs
  and/or
  (vii) Penetrates peritoneum.
(b) Extent of spread beyond bowel wall (mm) and clearance at deep excision margin (mm) to be measured on gross specimen and confirmed histologically.
(c) Involvement of proximal and distal margins of specimen requires histological confirmation only when the margins are close to the tumour (<3 cm) or tumour is highly infiltrative.
(d) State whether tumour excision is complete or incomplete.

3.3 Lymphatic spread.
(a) Number of nodes draining bowel segment harbouring tumour.
(b) Number of nodes with metastatic cancer.
(c) Metastasis in apical node (immediately below vessel ligature)
(d) Extramural tumour deposits apparently not within nodes.
(e) Lymphatic or perineural permeation (yes/no).

3.4 Venous spread.
Invasion of extramural veins.

3.5 Histology.
(a) Type (adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, other)
(b) Differentiation (poor or other).
(c) Invasive margin (expanding or infiltrating).
(d) Peritumoral lymphocytes (conspicuous or not).

3.6 Other pathology.
(a) Synchronous carcinoma.
(b) Adenoma.
(c) Other.

Clinicopathological classification

One of the principal aims of a tumour classification is to stratify patients into groups with differing prospects of cure. However, there is also a need to predict other clinical end-points, such as local recurrence, time to death or response to adjuvant therapy. Moreover, the clinician requires guidance at all stages in patient management. For example, it would obviously be advantageous to stage patients accurately before surgery. It is hoped that the prospective collection of data, standardized in the way recommended above, will facilitate the development of improved classifications which can be usefully applied at different stages of patient management.

With respect to postoperative staging classifications, it should be possible to develop in the future an improved prognostic grouping by identifying, using multivariate analysis, all variables that predict cancer-related death independently. These variables may relate not only to tumour stage, but also to other histological features or to clinical findings[15–17]. Until these improved classifications are defined and validated, it is recommended that after operation patients continue to be classified in the traditional way, the only difference being that the standardized pathological and clinical criteria described above should be employed. Thus, following pre-operative, operative and pathological assessments, patients should be designated as having operations which are *curative*, *non-curative* or *indeterminate for cure*.

Non-curative operations are those in which tumour has been left behind. The procedures should be categorized in two groups as follows:

(1) *Non-curative owing to the presence of distant metastases.* Whenever possible this must be supported by histological confirmation. The latter proviso may be waived when metastases are convincingly demonstrated on imaging, but biopsy is not desirable, e.g. lung metastases detected on chest X-ray.

(2) *Non-curative owing to the presence of residual local disease.* This may be confirmed by histological examination. Included in this category are those patients whose operative specimens on histological examination show tumour at any margin of excision. The only group in which histological confirmation of residual local disease is not required is when the specimen has been perforated, either spontaneously or operatively.

Curative operations are defined as those procedures in which the surgeon has removed all tumour, and this has been confirmed by pre-operative imaging assessment and postoperative histological examination of the specimen. Curative operations should be classified as follows:

A cases. The tumour is limited to bowel wall with no lymph node metastases.

B cases. The tumour extends beyond the bowel wall, i.e. muscularis propria, with no lymph node metastases.

C cases. Lymph node metastases demonstrated (extent of local spread irrelevant).

If there is any doubt, the patient should be classified as having an operation (specified) which is *indeterminate for cure*. The definition of curative can only be applied to operations in which the tumour has been resected together with a segment of bowel and its associated area of lymphatic drainage. Procedures in which the tumour is removed by local excision can only be classified as either non-curative or indeterminate.

Discussion

Whereas it is appreciated that there will be some dissent concerning these recommendations, the working party fervently hopes that they will be accepted by all those dealing with colorectal cancer. By so doing, uniformity of reporting will be improved and will help to make comparisons of trials more meaningful. It should be pointed out that these are interim recommendations. The Committee appreciates that there are promising technological advances such as endoluminal sonography[18,19] and hepatic flow scintigraphy[20], which have been shown to detect local spread of rectal cancer and occult hepatic metastases, respectively. Nevertheless, at the present time, these innovations need further evaluation before they can be generally accepted. It is hoped that such developments, together with the collection of extensive standardized data, will improve the clinicopathological classification of colorectal cancer. Unless data are collected in a standardized fashion, such improvements will not be forthcoming.

Acknowledgements

We are very grateful to Miss Janet Mutch for typing the manuscript

References

1 Second Report of an MRC Working Party. The evaluation of low-dose pre-operative X-ray therapy in the management of operable rectal cancer: results of a randomly controlled trial. *Br J Surg* 1984; **71**: 21–5.

2. Taylor I, Machin D, Mullee M *et al* A randomised controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985, **72**: 359–63.

3 Gastrointestinal Tumour Study Group. Prolongation of disease free interval in surgically treated rectal carcinoma *N Engl J Med* 1985; **312**: 1465–72.

4. Dukes CE The spread of cancer of the rectum. *Br J Surg* 1930; **17** 643.

5. Dukes CE. Cancer of the rectum; an analysis of 1000 cases *J Pathol Bacteriol* 1940, **50**. 527

6 Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Ann Surg* 1954; **139**: 846.

7 Kirklin JW, Dockerty MB, Waugh JM. The role of peritoneal reflection in the prognosis of carcinoma of the rectum and sigmoid colon. *Surg Gynecol Obstet* 1949; **88**: 326.

8. Beart RW Jr, Van Heerden JA, Beahr OH Evaluation in the pathological staging of carcinoma of the colon. *Surg Gynecol Obstet* 1978; **146**: 257.

9. Turnbull RB, Kyle K, Watson FB, Spratt J. Cancer of the colon: the influence of the no touch isolation technic on survival rates. *Ann Surg* 1967; **166**: 420.

10. Finlay IG, McArdle CS. The identification of patients at high risk following curative resection for colorectal carcinoma. *Br J Surg* 1982; **69**: 583–4.

11. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. *Lancet* 1986; **ii**: 996–8.

12. Wood CB, Gillis LR, Hole D *et al.* Local tumour invasion as a prognostic factor in colorectal cancer. *Br J Surg* 1981; **68**: 326–8

13. Durdey P, Williams NS The effect of malignant fixation of rectal carcinoma on prognosis after rectal excision. *Br J Surg* 1984; **71** 787–90.

14. Davis NC, Newland RC. The reporting of colorectal cancer. The Australian clinicopathological staging system. *Aust NZ J Surg* 1982; **52**: 395.

15 Chapuis PH, Dent OF, Fisher R *et al.* A multivariate analysis of clinical and pathological variables in resection of large bowel cancer. *Br J Surg* 1985; **72**: 698–702.

16. Fielding LP, Phillips RSK, Frye JS, Hittinger R. The prediction of outcome after curative resection for large bowel cancer. *Lancet* 1986; **ii**: 904–7

17. Jass JR, Love SB, Northover JMA. A new prognostic classification of rectal cancer. *Lancet* 1987; **i**. 1303–6.

18 Hildebrandt U, Fiefel G. Pre-operative staging of rectal cancer by intrarectal ultrasound. *Dis Colon Rectum* 1985; **28**: 42–6.

19. Benyon J, Foy DMA, Roe RM *et al* Endoluminal ultrasound in the assessment of local invasion of rectal cancer. *Br J Surg* 1986; **73**: 474–7.

20 Leveson SH, Wiggins PA, Giles GR, Parkin A, Robinson PJ. Deranged liver blood flow patterns in the detection of liver metastases. *Br J Surg* 1985, **72**: 128–30.

Paper accepted 29 February 1988

Appendix

The UKCCCR was formed in 1985 in order to co-ordinate the research activities of all of the major grant-awarding bodies involved in cancer research. Several sub-committees resulted, one of which was the colorectal sub-committee. The first task of this committee was to set up a working party to examine the assessment and staging of patients with colorectal cancer. The members of the working party are:

Mr N. C. M. Armitage, Dr S. J. Arnott, Mr J. Beynon, Dr M. F. Dixon, Mr P. Durdey, Professor L. P. Fielding, Mr L. Freedman, Mr J. J. Fry, Mr R. H. Grace, Professor J. D. Hardcastle (Chairman), Dr R. D. James, Dr J. R. Jass, Dr R. J. Johnson, Mr C. S. McArdle, Mr N. J. McC. Mortensen, Mr R. J. Nicholls, Mr J. M. A. Northover, Mr G. D. Oates, Mr R. K. S. Phillips, Mr N. H. Porter, Dr P. Quirke, Dr P. J. Robinson, Mr P. F. Schofield, Professor I. Taylor, Dr J. A. H. Waterhouse, Professor N. S. Williams (Secretary), Professor N. A. Wright.

Br. J. Surg. 1988, Vol. 75, July, 653–655

Natural history and treatment of anorectal strictures complicating Crohn's disease

L. Linares, L. F. Moreira, H. Andrews, R. N. Allan, J. Alexander-Williams and M. R. B. Keighley

Department of Surgery, The General Hospital, Birmingham B4 6NH, UK
Correspondence to:
Professor M. R B. Keighley

Forty-four patients seen between 1975 and 1985 with anorectal strictures complicating Crohn's disease have been reviewed to determine the natural history and outcome of surgical treatment. Proctitis was present in 98 per cent, and 93 per cent of patients had severe perianal disease. The site of strictures was rectal in 22, anal in 15 and anorectal in 11 (4 patients had a stricture at 2 sites). Initial treatment was by rectal excision alone in 6, dilatation in 33, and 5 needed no treatment at all. Single dilatation was effective in 15, 8 required two dilatations and in 10 repeated dilatation was necessary. Proctocolectomy was eventually required in 19 patients, 2 have a loop ileostomy and 1 has an ileostomy with a rectal stump in situ. *Only 21 remain asymptomatic while 3 continue to need dilatation. Perineal wound healing was delayed in 9 of 19 patients having a proctocolectomy and in 3 the perineal wound has never healed.*

Keywords: Anorectal stricture, Crohn's disease, perianal disease, dilatation, proctocolectomy, perineal wound healing

When Crohn described regional ileitis in 1932[1] he failed to mention the existence of perianal manifestations. Only quite recently has the importance of these complications been fully recognized[2]. Crohn's disease is often characterized by strictures in the small and large bowel, and the anorectum is not immune to this complication. Anal and rectal strictures are commonly associated with fissures and ulcers[3–5]. Anorectal strictures may also be found in other disorders, particularly ulcerative colitis, ischaemic colitis, venereal disease and following radiotherapy; hence an accurate assessment is essential to determine the underlying disorder[6,7]. Despite the presence of extensive narrowing in the anorectum, some patients with rectal strictures complicating Crohn's disease have no symptoms. Absence of difficulty with defaecation in some of these patients is probably because the stools tend to be softer owing to resection or ileal involvement by Crohn's disease.

Most clinicians adopt a conservative attitude towards the management of perianal Crohn's disease[4,8]. However, rectal excision may be necessary if the disease becomes so distressing that construction of a stoma is considered preferable to persistent perianal sepsis and long-standing intractable proctocolitis.

The aim of the present study has been to determine the site, natural history and results of treatment for patients with anorectal strictures complicating Crohn's disease.

Patients and methods

The records of 44 patients with anorectal strictures complicating Crohn's disease seen between 1975 and 1985 were reviewed. All patients had histopathological confirmation of Crohn's disease from rectal biopsy or had diagnostic radiological features of regional enteritis. Strictures were defined as stenotic areas which would not allow passage of a flexible or small rigid sigmoidoscope. Some patients with painful perianal disease could only be assessed during anaesthesia. The site of the stricture was classified into one of three anatomical sites, anal, anorectal and rectal[7]. Associated perianal disease and proctitis were recorded. Perianal lesions were classified according to the criteria defined by Hughes[4,5]

The incidence of previous operations for Crohn's disease was recorded. Operations were subdivided into ileocaecal, colonic resections or previous faecal diversion procedures alone. The method of dilatation was recorded and subdivided into three groups: digital dilatation, rigid dilatation using an endoluminal probe, or dilatation by coaxial balloon. Complications occurring after dilatation were recorded We also noted the time interval between the onset of disease and initial therapy. If treatment involved rectal excision, influence of the stricture on perineal wound healing was also assessed For this purpose perineal healing was classified as early healing if this was achieved within 4 weeks of operation, or delayed for those wounds which healed between 1 and 12 months after operation. All remaining wounds have remained unhealed

Results

Fifteen (34 per cent) of the forty-four patients were men. The mean age of the patients was 46 years (range 18–75 years). Sixteen patients had required previous surgical treatment. Previous operations included ileocaecal resection in 11, colectomy and ileorectal anastomosis in 6 and a proximal stoma in 5 (1 ileostomy and 4 colostomies). Of the 48 strictures, 22 were in the rectum, 15 were anal and 11 were anorectal. Four patients had a stricture at 2 sites. Proctitis was present in 43 patients (98 per cent) and perianal disease in 41 (93 per cent). Twenty-one patients (48 per cent) had an associated perianal abscess. Other manifestations of perianal Crohn's disease included a fissure or an ulcer in 20 patients (45 per cent), a fistula *in ano* in 18 (41 per cent) and skin tags in 18 (41 per cent). Fifty-nine per cent presented with their stricture in the second or third decade. Three patients developed strictures in childhood and only one of our patients presented over the age of 60 years.

The principal symptoms were bloody diarrhoea in 19, constipation in 14, severe perineal pain in 11 and incontinence in 12.

In 59 per cent of the patients, initial treatment of the stricture was undertaken within the first 10 years of the disease. The shortest interval between diagnosis and treatment was 1 month and the longest was 36 years.

Of the 44 patients under review, 5 have had no specific treatment other than medical therapy for proctitis using sulphasalazine, metronidazole and steroid enemas. None of these patients have required dilatation subsequently, and at the time of follow-up their proctitis is quiescent. Six patients had a primary rectal excision because of severe proctitis and extensive perianal disease in association with a rectal stricture One of these patients had a primary proctocolectomy due to the presence of an adenocarcinoma which was found in association with longstanding Crohn's disease complicated by perianal stricture. The remaining 33 patients underwent dilatation.

Dilatation was performed by gentle digital examination in 26 of 33 patients and 5 strictures were dilated using a coaxial

0007–1323/88/070653–03$3.00

Table 1 *Follow-up of the 44 patients under review*

Primary treatment	*n*	Follow-up	*n*
Medical therapy only	5	Asymptomatic (no stoma)	5
Initial proctocolectomy	6	Proctocolectomy	6
Dilatation	33	Ileostomy (rectum *in situ*)	1
		Proctocolectomy	13
		Loop ileostomy	3
		Repeat dilatation (no stoma)	2
		Asymptomatic (no stoma)	14

Table 2 *Perineal wound healing in the 19 patients who required rectal excision*

		Wound		
Stricture	Rectal excision	Healed (within 1 month)	Delayed (1–12 months)	Unhealed
No dilatation	6	3	3	0
Dilatation	13	4	6	3
Total	19	7	9	3

balloon technique. In the remaining two patients dilatation was achieved by Hegar (Rocket, London, UK) dilators. Fifteen patients required only a single dilatation, eight required two dilatations only and ten (30 per cent) required three or more dilatations. Follow-up of patients having anorectal dilatation has revealed that 14 remain asymptomatic and have not required any further therapy. Two patients still require occasional repeated dilatation and three have had a proximal loop ileostomy because of severe perianal sepsis. The remaining 14 patients have required more aggressive surgical treatment because of severe rectal and perianal disease. These operations have included proctocolectomy and ileostomy in 13 and colectomy with oversewing of the rectal stump and ileostomy in one (*Table 1*).

Six patients developed a perianal abscess or exacerbation of a perirectal fistula following dilatation. This event was presumably due to damage to the rectal wall associated with faecal contamination of the perirectal tissues. One further patient developed an *Escherichia coli* septicaemia lasting 24 h following rectal dilatation. There were no overt intraperitoneal perforations and no episodes of severe haemorrhage after dilatation.

A total of 19 patients eventually required rectal excision, 6 as initial therapy and 13 after repeated dilatation had failed to control the symptoms and complications of the rectal stricture. Following proctocolectomy only 7 of 19 patients achieved early perineal wound healing within 4 weeks of operation, 9 patients had delay of perineal wound healing from between 1 and 12 months following operation and in 3 patients the perineal wound has never healed (*Table 2*).

Discussion

Perianal Crohn's disease is now a well-recognized complication and often a presenting feature of regional enteritis[8,9]. There is a wide variation in the incidence of perianal Crohn's disease but it appears to be more common in patients with distal colorectal involvement[5,10–15].

Anorectal strictures are less common as a manifestation of perianal Crohn's disease and rarely give rise to symptoms unless they are complicated by perianal sepsis or fistulae[3,7,10,16]. Anorectal strictures complicating Crohn's disease may be quiescent for many years. This probably explains the long time interval between the onset of the disease and the clinical presentation. In some patients strictures occur at more than one site and this was certainly the case in four of our patients. We have found that the majority of strictures occur in the rectum. However, precise definition of the location of these strictures may be difficult particularly if they are long and the anatomy of the anal canal is severely distorted by perianal sepsis, fistulae or previous anal surgery. Our own survey confirms the findings of other authors concerning the very high incidence of proctitis in patients with Crohn's strictures. Furthermore, other perianal manifestations are almost uniform among patients with anorectal strictures. Particularly common are abscesses, fistulae, fissures and skin tags[11,16,17].

In some series the presence of rectal stricture is associated with recto- or anovaginal fistulae. However, this complication was not apparent in any of our patients[18,19].

The presence of a carcinoma complicating a rectal stricture in this series is interesting since it is likely that long-standing untreated Crohn's proctitis may be complicated by malignant change[6].

Like many reports in the literature, all of our patients requiring treatment by dilatation had severe symptoms[7,11,16,17,20]. Dilatation was complicated by abscess or relapse of an anorectal fistula in six patients. In these patients it is likely that the dilatation caused damage to the bowel wall resulting in faecal contamination of the pararectal tissues.

A total of 19 patients eventually required proctocolectomy. Perineal wound healing was severely delayed in 9 of 19 patients and in 3 subjects the perineal wound has never healed. This incidence of delayed perineal wound healing is higher than in a previous survey from this hospital[21]. However, we believe that the presence of severe perianal disease and rectal strictures constitutes a high risk group in whom delayed perineal wound healing is a common phenomenon. We have examined the proctocolectomy rate in patients with anorectal strictures. The incidence of proctocolectomy in patients having initial dilatation was 16 per cent at 10 years and 34 per cent at 20 years.

We would advocate conservative therapy in patients with rectal stricture associated with minimal symptoms. Treatment usually consists of topical steroids, sulphasalazine and metronidazole. However, the evidence that metronidazole is particularly beneficial in this form of perianal disease is lacking[22–24]. If patients present with severe perianal disease in the presence of an anorectal stricture associated with severe symptoms or a fistula, immediate proctocolectomy does seem a reasonable option but patients should be warned that there is a risk of impaired perineal wound healing. It is preferable to perform a proctocolectomy when there is minimal perianal sepsis, and if contamination occurs at the time of operation it is probably wise to leave the perineal wound open to granulate rather than to attempt primary suture.

Although few patients in this survey underwent loop ileostomy alone, the technique may have some merit in patients with severe perianal disease complicated by anorectal stricture. There is no fear of delayed perineal wound healing using a proximal ileostomy and the operation may be performed without laparotomy. However, loop ileostomy or split ileostomy[25] may encourage further reduction in the lumen of the rectum since the faecal stream is divided. On the other hand, faecal diversion usually successfully controls obstructive symptoms, urgency, incontinence and soiling associated with the anorectal disease.

These results seem to indicate that anorectal strictures are a common manifestation of severe anorectal Crohn's disease. A few patients require no specific therapy. The majority can be managed by one or two dilatations. However, if repeated dilatations are necessary, most of these patients will either require a proctocolectomy or, if minimal surgery is desirable, a loop ileostomy may control symptoms and avoid the problem of an unhealed perineal wound.

References

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. a pathogenic and clinical entity *JAMA* 1932; **99**: 1323–9.

2. Yarnis H, Marshak RH, Crohn BB. Ileocolitis. *JAMA* 1957; **164**: 7–11.
3. Buchmann P, Alexander-Williams J. Classification of perianal Crohn's disease. *Clin Gastroenterol* 1980; **9**: 323–30.
4. Hughes LE. Surgical pathology and management of anorectal Crohn's disease. *J R Soc Med* 1978; **71**: 644–51.
5. Hughes LE, Jones IRG. Perianal lesions in Crohn's disease In Allan RN, Keighley MRB, Alexander-Williams J, Hawkins C, eds. *Inflammatory Bowel Diseases*. 1st ed. Edinburgh: Churchill Livingstone, 1983: 321–31.
6. DeDombal FT, Watts J McK, Watkinson G, Goligher JC. Local complications of ulcerative colitis: stricture, pseudopolyposis and carcinoma of colon and rectum. *Br Med J* 1966; **i**: 442–7.
7. Greenstein AJ, Sachar DB, Kark AE. Stricture of the anorectum in Crohn's disease involving the colon. *Ann Surg* 1975; **181**: 207–12.
8. Morson BK, Lockhart-Mummery HE. Anal lesions in Crohn's disease. *Lancet* 1959; **ii**· 1122–3.
9. Editorial. Anorectal Crohn's disease. *Br Med J* 1976; **ii**: 1341
10. Alexander-Williams J. The place of surgery in Crohn's disease. *Gut* 1971; **12**: 739–49.
11 Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology* 1975; **68**: 627–35.
12. Rankin GB, Watts HD, Melnyk CS, Kelly ML Jr. National Co-operative Crohn's Disease Study: extra-intestinal manifestations and perineal complications. *Gastroenterology* 1979; **77**: 914–20.
13. Williams NS, Macfie J, Celestin LR. Anorectal Crohn's disease. *Br J Surg* 1979; **66**: 743–8.
14. Williams DR, Coller JA, Corman ML, Nugent FW, Veidenheimer MC. Anal complications in Crohn's disease. *Dis Colon Rectum* 1981; **24**: 22–4.
15. Lockhart-Mummery HE Anal lesions in Crohn's disease *Br J Surg* 1985; **72**(Suppl): S95–S96.
16. Alexander-Williams J Fistula-in-ano: management of Crohn's fistula. *Dis Colon Rectum* 1976; **19**: 518–19.
17. Miles RPM. Benign strictures of the rectum. *Ann R Coll Surg Engl* 1972; **50**: 310–11.
18. Marks CG, Ritchie JK, Lockhart-Mummery HE. Anal fistulas in Crohn's disease. *Br J Surg* 1981; **68**: 526–7.
19. Tuken PA, Castro AF. Rectovaginal fistula in Crohn's disease. *Dis Colon Rectum* 1979; **22**: 58–62
20. Barber KW, Waugh JM, Beahrs OH, Sauer WG. Indications for and the results of surgical treatment of regional enteritis *Ann Surg* 1962; **156**: 472–82.
21. Scammell BE, Keighley MRB. Delayed perineal wound healing after proctectomy for Crohn's colitis *Br J Surg* 1986; **73**: 150–2
22. Bernstein LH, Frank MS, Brandt LJ, Boley JS. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**. 357–65.
23. Brandt LJ, Bernstein LH, Boley SJ, Frank MS Metronidazole therapy for perianal Crohn's disease· a follow-up study. *Gastroenterology* 1972; **83**· 383–7.
24. Hatoff DE. Perineal Crohn's disease complicated by pyogenic liver abscess during metronidazole therapy *Gastroenterology* 1983, **85**: 194–5.
25. Harper PH, Truelove SC, Lee ECG, Kettlewell MEW, Jewell DP. Split ileostomy and ileocolostomy for Crohn's disease of the colon and ulcerative colitis: a 20-year survey. *Gut* 1983; **24**· 106–13

Paper accepted 28 February 1988

Br. J. Surg. 1988, Vol. 75, July,
656–660

Role of constipation and anal hypertonia in the pathogenesis of haemorrhoids

C. P. Gibbons,
J. J. Bannister and
N. W. Read*

University Department of Surgery,
Royal Hallamshire Hospital,
Glossop Road, Sheffield S10 2JF,
*UK and *Department of*
Physiology, University of Sheffield,
UK
Correspondence to:
Mr C P. Gibbons, Ward A1,
University Hospital of Wales,
Heath Park, Cardiff CF4 4XW, UK

The hypothesis that haemorrhoids result from chronic constipation was investigated by studying bowel habit, anal pressure profiles and anal compliance in 13 men and 10 women with prolapsing haemorrhoids, 12 women with severe constipation and 14 male and 11 female control subjects. Defaecation was less frequent in women than in men ($P<0{\cdot}01$) *but was independent of the presence of haemorrhoids. Patients with haemorrhoids and control subjects reported similar stool consistency and rarely admitted to straining. Severely constipated women complained of infrequent defaecation, straining at stool and hard motions, but none had prolapsing haemorrhoids. Haemorrhoids were associated with significantly longer anal high-pressure zones and significantly greater maximum resting pressures at all levels of anal distension* ($P<0{\cdot}01$), *but minimum residual pressure during rectal distension and maximum squeeze pressure were not significantly different from control subjects. Maximum resting pressure was increased in patients of both sexes with haemorrhoids, but this reached statistical significance only in men* ($P<0{\cdot}001$). *Constipated women had normal anal pressure profiles and maximum anal pressures. These data show that patients with haemorrhoids are not necessarily constipated but tend to have abnormal anal pressure profiles and anal compliance. Chronically constipated women do not necessarily have haemorrhoids but have normal anal pressure profiles and compliance. This casts doubt upon the hypothesis that haemorrhoids are caused by constipation*

Keywords: Anal sphincter pressure, constipation, haemorrhoids

Constipation has long been implicated in the pathogenesis of haemorrhoids[1,2] but evidence of a causal relationship is circumstantial. Indeed, data available on the bowel habit of patients with symptomatic haemorrhoids provide little support for this hypothesis[3,4].

Anal sphincter pressure is known to be elevated in the presence of haemorrhoids[3,5–11] and it has been proposed that an increased sphincter tone may have a pathogenic role in the hypertrophy of the anal cushions. Alternatively, increased anal sphincter pressure could be a result of constant distension of the anal sphincters by the bulk of the haemorrhoids. Anal sphincter compliance, estimated by measuring anal pressure at different levels of anal distension, gives more information on the mechanical properties of the anus[12] and thereby may help to determine the relative contributions of sphincter tone and passive stretching of the sphincter muscle to the elevation of sphincter pressure in patients with haemorrhoids.

In an attempt to determine the inter-relationships of constipation and anal hypertonia in the pathogenesis of haemorrhoids, the bowel habit and anal compliance characteristics of 23 patients with symptomatic second- or third-degree haemorrhoids were compared with those of 25 normal subjects and 12 patients with severe constipation.

Patients and methods

Patients

Thirteen male patients (aged 47·6 years ±12·6 s.d.) and ten female patients (aged 58·1 years ±12·1 s.d.) presenting with symptomatic prolapsing haemorrhoids and twelve severely constipated women (aged 37·8 years ±10·8 s.d.) were studied. Fourteen normal men (aged 41·2 years ±13·4 s.d.) and 11 normal women (aged 44·7 years ±13·4 s.d.) were used as control subjects. All subjects and patients completed a questionnaire on their past medical history, bowel habit and symptoms and were subjected to proctoscopy before manometric studies. Only patients with second- or third-degree haemorrhoids were included in the haemorrhoid group and none of the control or constipated groups had second-, third- or symptomatic first-degree haemorrhoids. A 13th female patient presenting with chronic constipation was found to have second-degree haemorrhoids on proctoscopy and was excluded from the analysis. None of the patients or controls had clinical evidence of perineal descent on straining. No patient or control subject had taken any laxative medication within a week of the study. Bowel preparation was not used but the subjects were invited to defaecate before the test should they feel the desire to do so. The study was approved by the Ethical Committee of the Royal Hallamshire Hospital, Sheffield on 3 October 1983

Recording methods

The manometric recording methods have been described in detail elsewhere[12]. In brief, a series of rigid cylindrical probes, 1·0–3·0 cm in diameter, and a semi-rigid probe, 0·4 cm in diameter, each carrying four polyvinyl tubes of internal diameter 1·14 mm and arranged radially at 90° with side openings near the tip of the probe, were used. Each tube was continuously perfused using degassed water and incorporated in the infusion line was a pressure transducer, the output of which was amplified and displayed on a chart recorder.

With the patient in the left lateral position, an inflatable balloon connected to a narrow catheter (1·5 mm outside diameter) was inserted into the lower rectum via a proctoscope. A lubricated 0·4 cm recording probe was introduced into the anal canal with the side holes in the anterior, posterior and lateral positions. After 30 s, recordings were made at 1 cm stations on insertion and withdrawal, allowing 15 s at each station for stabilization. The mean of the four radial pressures at each station on insertion and withdrawal was used to construct the anal pressure profile at rest. The highest pressure reached in the resting pressure profile was the resting anal sphincter pressure used to construct the anal compliance curves. Next, a squeeze pressure profile was obtained on re-insertion by calculating the mean of the peak pressures obtained during each of two 10 s maximum voluntary external sphincter contractions at each station allowing 15 s for stabilization between

Table 1 *Bowel habit review in male and female patients with haemorrhoids, female patients with severe idiopathic constipation and normal control subjects*

				Hard stool (n)			Straining (n)		
Sex	Condition	No. of subjects	Bowel frequency (per week)*	Usual	Occasional	Never	Usual	Occasional	Never
Male	Control	14	9·6±1·4	0	3	11	0	5	9
	Haemorrhoids	13	10·4±1·5	0	3	10	0	3	10
Female	Control	11	6·8±0·3	0	7	4	0	2	9
	Haemorrhoids	10	6·1±0·8	3	1	6	3	3	4
	Constipated	12	1·0±0·2	9	0	3	11	0	1

* Mean ± s.e.m. Analysis of variance: bowel frequency of men *versus* women, $P<0{\cdot}01$; haemorrhoids *versus* controls, not significant

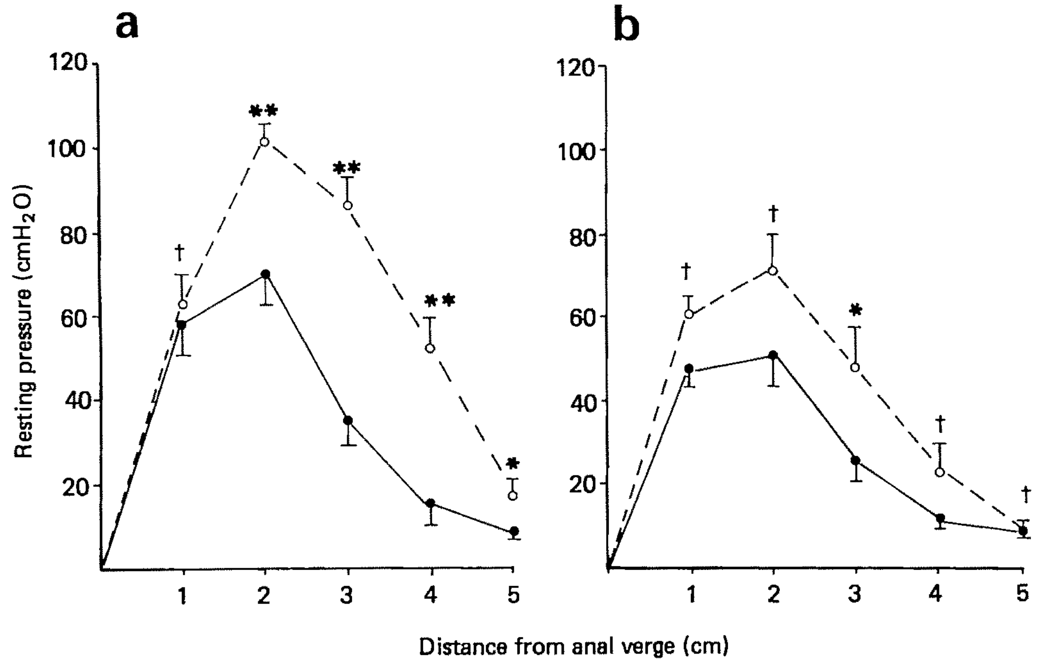


Figure 1 *Resting pressure profiles of* **a** *13 male patients with prolapsing haemorrhoids and 14 normal male subjects, and* **b** *10 female patients with prolapsing haemorrhoids and 11 normal female control subjects, using the smallest-diameter recording probe (0·4 cm). Each point represents mean ± s.e.m of observations at each station. Comparison of patients with haemorrhoids (○) and normal subjects (●): * P<0·05, ** P<0·001, † not significant (Student's t test)*

contractions. The highest pressure reached in the squeeze pressure profile was used to construct the anal compliance curve during external sphincter contraction. Then, with the probe at the point of maximum resting pressure, the minimum residual pressure attained during a 1 min inflation of the rectal balloon with 100 ml air was calculated. The whole procedure was repeated using the 1 cm and 2 cm diameter probes.

Treatment of results

The mean ± s.e.m. of the maximum anal pressures at rest was plotted against probe diameter to give the compliance curve for each group. Similar compliance curves were obtained for maximum squeeze pressure and for minimum residual pressures (during rectal distension). Comparisons were made between groups by analysis of variance.

Results

Bowel habit

As shown in *Table 1*, women had significantly less frequent bowel actions than men ($P<0{\cdot}01$) but there was no significant difference between patients with haemorrhoids and control subjects (by analysis of variance). Similar numbers of haemorrhoid patients and control subjects admitted to occasional hard stools and straining, although in three of the female haemorrhoid patients this occurred regularly. The severely constipated women had less frequent bowel actions and most of them regularly had hard stools and strained, despite a diet supplemented with at least 30 g crude fibre per day plus intermittent laxatives.

Anal pressure profiles

Resting pressure profiles of patients with haemorrhoids and control subjects are compared in *Figure 1*. Maximum resting pressures were significantly greater in patients with haemorrhoids than in control subjects ($P<0{\cdot}01$) and in male than in female patients ($P<0{\cdot}01$) when compared by analysis of variance. In women the increase in resting pressure associated with haemorrhoids was less marked than in men and failed to reach statistical significance when considered in isolation. Patients with haemorrhoids had significantly longer ($P<0{\cdot}01$) anal high-pressure zones than control subjects (*Table 2*). This effect was again more marked for men than women. However, there was no significant difference between the sexes in length of the high-pressure zone. Squeeze pressure profiles (*Figure 2*) revealed a similar maximum pressure for haemorrhoid patients and controls with no significant difference in the length of the high-pressure zone. In constipated women, resting and squeeze pressure profiles and the length of the anal high-pressure zone, were similar to those of female control subjects (*Figure 3* and *4*; *Table 2*).

Anal compliance characteristics

Anal compliance curves were similar in shape in the presence and absence of haemorrhoids (*Figure 5*) or constipation (*Figure 6*). Maximum resting pressure increased ($P<0{\cdot}001$) with probe diameter, was greater in men than in women ($P<0{\cdot}001$) and greater in patients with haemorrhoids than in control subjects ($P<0{\cdot}01$) by analysis of variance. Maximum squeeze pressure increased with probe diameter ($P<0{\cdot}001$), was greater in men than in women ($P<0{\cdot}001$) but was not significantly different in the presence of absence of haemorrhoids, although the female, patients with haemorrhoids tended to have lower squeeze pressures than controls. Minimum residual pressures during rectal distension increased with probe diameter ($P<0{\cdot}001$) but were not significantly different between men and women, nor between patients with or without haemorrhoids. There was no significant difference in resting pressures, squeeze pressures or minimum residual pressures between constipated and control women.

Discussion

This study fails to show any significant difference in frequency, consistency or ease of defaecation between patients with haemorrhoids and normal subjects. The absence of a definite history of constipation or regular straining in the majority of patients with haemorrhoids is evidence against the role of these disorders of bowel habit in the pathogenesis of haemorrhoids as suggested by Burkitt[1] and Graham-Stewart[2]. Hancock[3] also failed to find a significant difference in bowel frequency between haemorrhoid patients and controls, but 57 per cent of his patients admitted to straining, in comparison with 20 per cent of controls. Nevertheless, 43 per cent of his patients never strained and 59 per cent had not strained before the onset of haemorrhoidal bleeding or prolapse, which suggests that straining is more likely to be a consequence than the cause of haemorrhoids. A further argument against an aetiological role for constipation in the formation of haemorrhoids is that symptomatic piles are less common in women[13], who defaecate less frequently and strain more often, and are rare in women with severe constipation.

Table 2 *Length of the high-pressure zone in control subjects, patients with haemorrhoids and women with severe constipation*

Sex	Condition	No. of subjects	Length of HPZ (cm)	
Male	Control	14	3·2±0·3	
	Haemorrhoids	13	4·7±0·2	$P<0{\cdot}001$*
Female	Control	11	3·2±0·3	
	Haemorrhoids	10	3·7±0·3	n.s.†
	Constipation	11	3·3±0·1	n.s.†

HPZ, high-pressure zone. The mean±s.e.m. length of the HPZ is given in each case. Analysis of variance of the top four groups showed that the difference in length of the HPZ associated with haemorrhoids was statistically significant ($P<0{\cdot}01$) whereas that associated with sex was not significant. * P for difference from control by Student's t test; † P for difference from control by Dunnett's t test

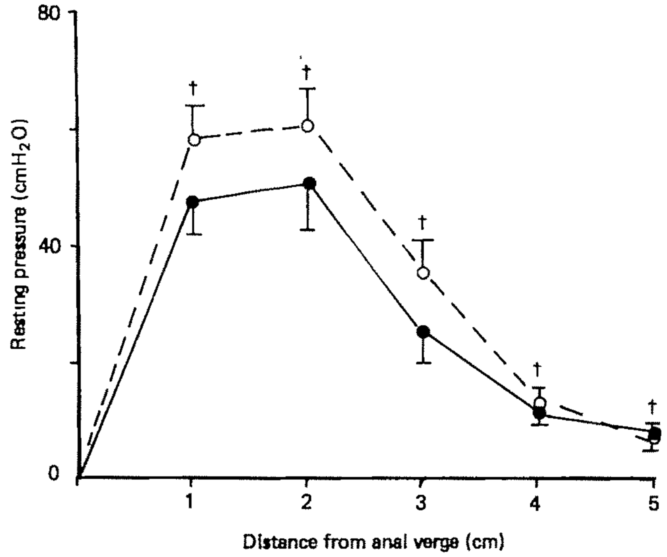


Figure 3 *Resting pressure profiles of 12 female patients with severe constipation* (○) *and 11 normal female control subjects* (●), *using the 0·4 cm diameter recording probe. Each point represents mean±s.e.m. of observations at each station.* † *Difference between control subjects and those with severe constipation at each station, not significant* (*Student's* t *test*)

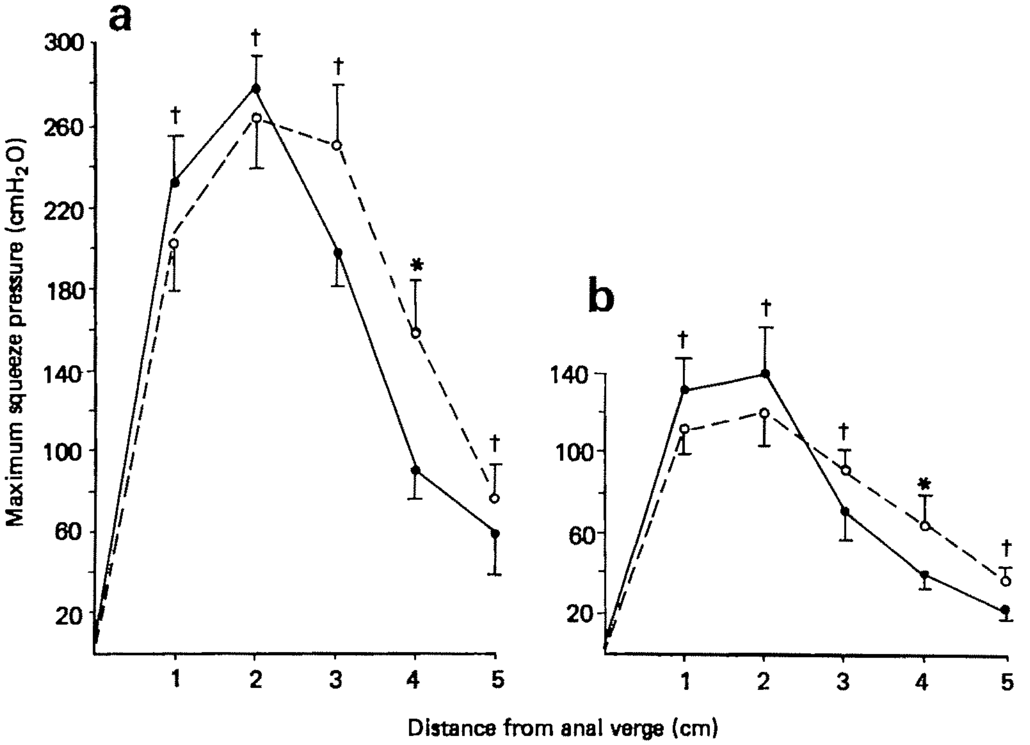


Figure 2 *Squeeze pressure profiles of* **a** *13 male patients with prolapsing haemorrhoids and 14 normal male subjects, and* **b** *10 female patients with prolapsing haemorrhoids and 11 normal female control subjects using the 0·4 cm diameter recording probe. Each point represents mean±s.e.m. of observations at each station. Comparison of patients with haemorrhoids* (○) *and normal subjects* (●): * $P<0{\cdot}05$, † *not significant* (*Student's* t *test*)

It has been shown in several studies[3,5-11] that maximal resting anal pressure is elevated in patients with haemorrhoids. Our data confirm and extend this finding, showing in addition that the resting anal compliance curve is displaced upwards and that the length of the high-pressure zone is increased. It appears unlikely that the elevation in resting pressure is attributable to passive stretching of the anal sphincter muscle by the haemorrhoidal bulk, because this would be expected to produce a shift to the left rather than an upward displacement of the compliance curve. The data favour an increase in internal sphincter tone, as suggested by Hancock[3], rather than external sphincter hypertrophy as suggested by Teramoto *et al.*[14], especially as maximal squeeze pressures (under conditions of maximal external sphincter contraction) and minimum residual pressures (during internal sphincter inhibition) were similar in patients with haemorrhoids, and in controls.

In our study the increase in resting anal sphincter pressure associated with haemorrhoids was less in women than men,

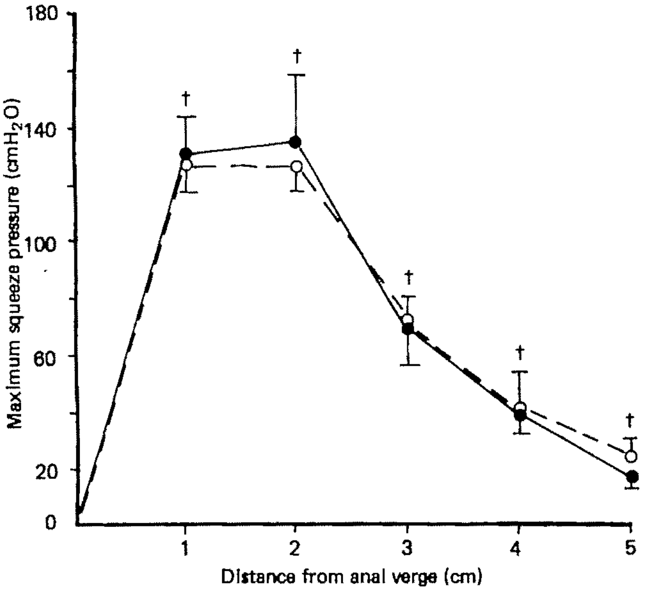


Figure 4 *Squeeze pressure profiles of 12 female patients with severe constipation (○) and 11 normal female control subjects (●), using the 0·4 cm diameter recording probe. Each point represents mean ± s.e.m. of observations at each station* † *Difference between control subjects and those with severe constipation at each station, not significant (Student's* t *test)*

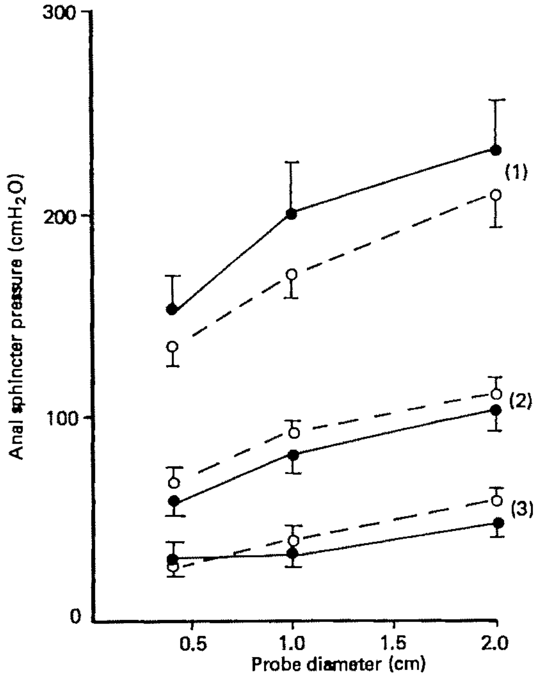


Figure 6 *Anal compliance curves of 12 female patients with severe constipation (○) and 11 normal female control subjects (●) under conditions of (1) maximum external sphincter contraction (squeeze), (2) rest, and (3) internal sphincter relaxation (minimum residual pressure during inflation of a 100 ml rectal balloon while recording at the point of maximum resting pressure) Each point represents mean ± s.e.m. of maximum sphincter pressures obtained for patients of each group at each probe diameter*

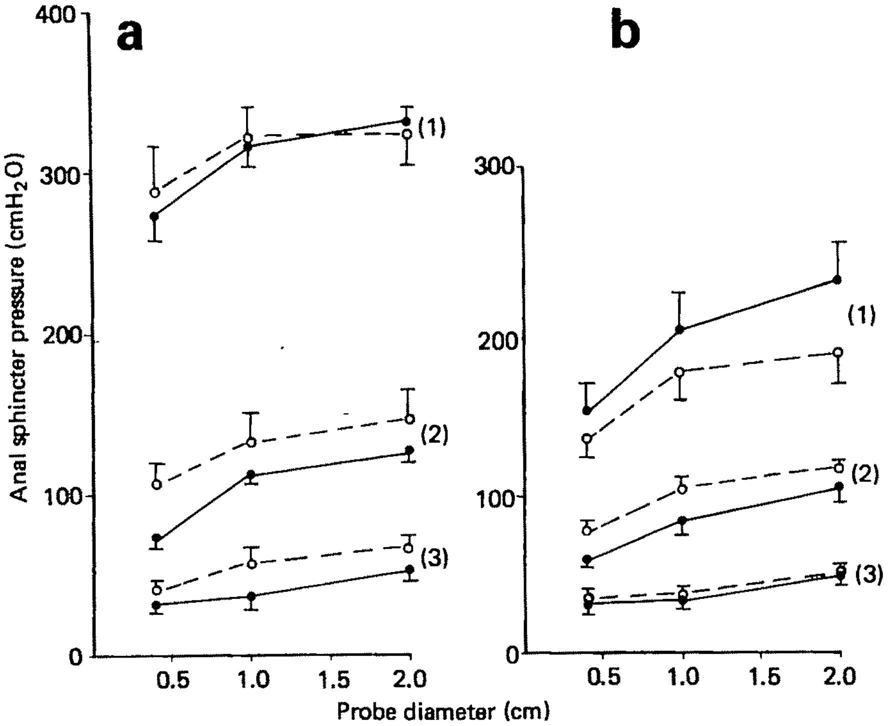


Figure 5 *Anal compliance curves of* **a** *13 male patients with prolapsing haemorrhoids (○) and 14 normal male subjects (●) and* **b** *10 female patients with prolapsing haemorrhoids (○) and 11 normal female control subjects (●) under conditions of (1) maximum external sphincter contraction (squeeze), (2) rest, and (3) internal sphincter relaxation (minimum residual pressure during inflation of a 100 ml rectal balloon while recording at the point of maximum resting pressure). Each point represents mean ± s.e.m. of maximum sphincter pressures obtained for patients of each group at each probe diameter*

failing to reach statistical significance in women. This is similar to the results of Arabi *et al.*[6]. Most other reports of anal sphincter pressure in haemorrhoids fail to categorize the results according to sex[3,7–10]. However, Read *et al.*[7] did find a highly significant increase in anal sphincter pressure in haemorrhoids using groups of patients and controls with a strong female bias (F:M ratios 15:4 and 18:3 respectively) and Deutsch *et al.*[11] reported significantly greater sphincter pressures in women with haemorrhoids than in female controls, although the data presented by the latter group are somewhat confusing. It seems likely, therefore, that the anal sphincter pressure is, indeed, elevated in the presence of haemorrhoids in both sexes.

The length of the anal high-pressure zone was found to be increased in patients with haemorrhoids. Two recent studies which included anal pressure profiles of patients with haemorrhoids and of control subjects also showed a lengthening of the high-pressure zone but this was not commented upon by the authors[9,10]. The relevance of this observation to the pathogenesis of haemorrhoids, however, is uncertain.

Constipation does not appear to cause anal hypertonia, as our group of severely constipated women had normal anal pressure profiles and anal compliance. Abnormal anal pressures and compliance do not necessarily lead to haemorrhoid formation, because patients with anal fissures have very high resting anal pressures[15] but do not necessarily develop prolapsing haemorrhoids. Moreover, the prevalence of haemorrhoids increases with age[16], whereas the anal sphincter pressure tends to decrease[17].

We therefore conclude that the decrease in anal compliance, the increase in anal sphincter pressure and the lengthening of the anal high-pressure zone seen in patients with haemorrhoids are attributable to a change in the tone of the internal anal sphincter occurring coincidentally with, or subsequent to, the hypertrophy of the anal cushions, rather than as a result of passive stretching of the sphincter by the increased bulk of the anal lining. Moreover, these effects do not appear to be related to any change in bowel habit.

References

1. Burkitt D. Varicose veins, deep vein thrombosis and haemorrhoids. Epidemiology and suggested aetiology. *Br Med J* 1972; **ii**: 556–61.
2. Graham-Stewart CW. Injection treatment of haemorrhoids *Br Med J* 1962, **i**: 213–16.
3. Hancock BD. Internal sphincter and the nature of haemorrhoids *Gut* 1977, **18**: 651–5.
4. Thompson JPS, Leicester RJ. Haemorrhoids: pathophysiology and clinical features. In: Henry MM, Swash M, eds. *Coloproctology and the Pelvic Floor: Pathophysiology and Management* London: Butterworths, 1985. 195–216.
5. Hancock BD, Smith K. The internal sphincter and Lord's procedure for haemorrhoids. *Br J Surg* 1975; **62**: 833–6.
6. Arabi Y, Alexander-Williams J, Keighley MRB. Anal pressures in hemorrhoids and anal fissure. *Am J Surg* 1977; **134**: 608–10.
7. Read NW, Bartolo DCC, Read MG, Hall J, Haynes WG, Johnson AG Differences in anorectal manometry between patients with haemorrhoids and patients with the descending perineum syndrome: implications for management *Br J Surg* 1983, **70**: 656–9.
8. Hiltunen K-M, Matikainen M. Anal manometric findings in symptomatic hemorrhoids. *Dis Colon Rectum* 1985; **28**: 807–9.
9. El-Gendi MAF, Abdel-Bakey N. Anorectal pressure in patients with symptomatic hemorrhoids. *Dis Colon Rectum* 1986, **29**: 388–91.
10. Schouten WR, van Vroonhoven TJ Lateral internal sphincterotomy in the treatment of hemorrhoids: a clinical and manometric study. *Dis Colon Rectum* 1986; **29**: 869–72.
11. Deutsch AA, Moshkovitz M, Nudelman I, Dinari G, Reiss R. Anal pressure measurements in the study of hemorrhoid etiology and their relation to treatment. *Dis Colon Rectum* 1987; **30**: 855–7.
12. Gibbons CP, Bannister JJ, Trowbridge EA, Read NW. An analysis of anal sphincter pressure and compliance in normal subjects. *Int J Colorect Dis* 1986, **1**: 231–7
13. Goligher JC. *Surgery of the Anus, Rectum and Colon*, 4th edn. London: Baillière-Tindall, 1980
14. Teramoto T, Parks AG, Swash M Hypertrophy of the external sphincter in haemorrhoids: a histometric study *Gut* 1981; **22**: 45–8.
15. Gibbons CP, Read NW. Anal hypertonia in fissures: cause or effect? *Br J Surg* 1986; **73**: 443–5.
16. Haas PA, Fox TA, Haas GP. The pathogenesis of haemorrhoids. *Dis Colon Rectum* 1984, **27**: 442–50.
17. Bannister JJ, Abouzekry L, Read NW. The effect of ageing on anorectal function. *Gut* 1987, **28**: 353–7.

Paper accepted 22 February 1988

Br. J. Surg. 1988, Vol. 75, July, 661–663

Lateral division of the puborectalis muscle in the management of severe constipation

M. A. Kamm*, P. R. Hawley and J. E. Lennard-Jones

St. Mark's Hospital, City Road, London EC1V 2PS, UK

Correspondence to:
Dr M. A. Kamm

Patients with severe constipation often do not 'relax' their pelvic floor during defaecation. Electromyography of the pelvic floor may reveal inappropriate contraction during defaecation straining, and balloon expulsion, a test of rectal evacuation, may be impaired. Fifteen patients with severe idiopathic constipation and three patients with a megarectum underwent lateral division of the puborectalis muscle and upper half of the external sphincter muscle. Twelve patients had a unilateral division and six patients had both sides divided. Surgery caused a marked reduction in the maximum voluntary squeeze pressure in the anal canal from a pre-operative mean of 90 ± 49 (s.d.) cmH_2O to a postoperative mean of $40 \pm 29\,cmH_2O$ ($P < 0{\cdot}0001$). Four patients, three with idiopathic constipation and one with megarectum, experienced symptomatic improvement. Three of these patients had a bilateral division. Improvement did not correlate with a change in the puborectalis electromyography or the ability to expel a balloon. Three patients experienced mild mucus or urge incontinence, but no patient was incontinent for solid stool.

Keywords: Constipation, puborectalis division

Severe constipation is a cause of considerable disability and is often very difficult to treat. In young patients, in whom the barium enema is normal, there is often marked insensitivity to laxatives[1]. In other patients the rectum, and sometimes the colon, is dilated. Both of these groups of patients describe marked difficulty with rectal evacuation, and recently developed techniques have demonstrated abnormalities in defaecatory function. In tests of simulated defaecation, patients with severe idiopathic constipation are often unable to expel a barium[2] or water-filled[3] balloon, or a saline enema[4] from the rectum. Electromyography of the pelvic floor striated muscle shows that there is often inappropriate increased activity of these muscles during defaecation straining[4–6].

The puborectalis muscle is considered to be one of the major contributors to the mechanism of continence. Its failure to relax during defaecation has been postulated as a cause of impaired evacuation, but previous posterior division of this muscle and the upper half of the external sphincter muscle failed to achieve the desired improvement in defaecation in patients with constipation[7]. Lateral internal sphincterotomy has proved a much more satisfactory operation than dorsal internal sphincterotomy in the treatment of chronic anal fissure[8]. For this reason it was decided to divide the puborectalis muscle and external anal sphincter in the lateral quadrant. The operation was performed in patients with severe idiopathic constipation and patients with megarectum who complained of difficulty with rectal evacuation and in whom electromyography and functional testing suggested an evacuation abnormality.

Patients and methods

Patients

Severe idiopathic constipation Fifteen female patients with a mean age at operation of 34 years (range 19–60, median 27·5) had severe idiopathic constipation. The mean length of history was 12 years (range 1–58). One patient dated the onset of constipation to early childhood, the remainder dated the onset to adolescence or adulthood One patient experienced the onset of constipation after gynaecological surgery while in another it followed Ivalon rectopexy for prolapse, in the remainder there was no known precipitating event. Two patients had previously had a colectomy with ileorectal anastomosis, one patient had had a segmental colonic resection, one patient had had an internal sphincterotomy followed by a colectomy, and one patient had had two manual dilatations.

In all the patients with an intact colon it was of normal size on barium enema The intestinal transit rate was assessed pre-operatively in 13 patients by a plain abdominal radiograph taken 5 days after the ingestion of 20 radio-opaque markers[9]. Eleven of these patients demonstrated prolonged transit, as evidenced by the retention of more than 20 per cent of the markers, while the transit in two patients was normal. A total of five patients had a normal stated pre-operative bowel frequency but were disabled by symptoms of straining and inability to evacuate the rectum.

Metabolic causes of constipation had been excluded, and Hirschsprung's disease had been excluded by confirming the presence of the recto-anal inhibitory reflex.

All the patients complained of marked difficulty with rectal evacuation and prolonged straining at stool. The mean stated pre-operative bowel frequency was once per 10 2 days (range twice per day to once per 4 weeks, median 7 days). Eleven patients used regular laxatives pre-operatively.

Megarectum. Three female patients had a megarectum and sigmoid on barium enema. They were aged 16, 17 and 24 years, and all had had symptoms of constipation since childhood. One of these patients had had a previous Duhamel procedure, and this patient also experienced faecal soiling before puborectalis division. The pre-operative bowel frequency for these patients was once every 7, 14 and 21 days, always with the assistance of laxatives. They also suffered from an inability to evacuate the rectum and prolonged straining at stool. Two of the three patients were tested and showed prolonged transit

Methods

All patients had pre-operative anorectal physiology studies and 16 patients had them postoperatively, performed by one investigator (M.K.). All patients were interviewed (by M K.).

Balloon expulsion. In a test of simulated defaecation with the patient lying on the left side, a lubricated rubber balloon attached to a plastic catheter was inserted to lie in the rectal ampulla. The balloon was filled with 50 ml of water and the patient was asked to strain and expel the balloon

---

* *Supported by the St. Mark's Research Foundation*

Table 1 *Results of lateral puborectalis division*

	Pre-operative	Postoperative
Mean stated bowel frequency	1/10 2 days	1/9·9 days
Median stated bowel frequency	1/8·5 days	1/7 0 days
Prolonged intestinal transit rate (>4/20 shapes retained at 5 days)	13/15	—
Normal intestinal transit rate	2/15	—
Straining at stool	17/18	15/18
Regular laxative use	14/18	12/18
Paradoxical contraction or no change on puborectalis EMG	15/16	12/16
Balloon expulsion positive	1/16	6/16
Anal canal pressure (mean ± s.d. cmH_2O)		
At rest	87±32	95±35*
Maximum squeeze (increment above resting pressure)	90±49	40±29†

Student's *t* test. * n s.; † $P<0·0001$. EMG, electromyography

Puborectalis electromyography. With the patient lying on the left side, a concentric needle electrode for recording muscle activity was introduced in the midline 12 mm posterior to the anal margin and directed slightly anteriorly. Recordings were made with the patient at rest and with the patient straining.

Anal manometry. With the patient lying on the left side, a 4 mm diameter water-filled latex balloon connected to a pressure transducer was used to measure the maximum anal canal pressures at rest and during voluntary contraction of the anal muscles A slow pull-through technique was used, with recordings taken every 0·5 cm along the anal canal.

Surgical technique

With the patient in the lithotomy position, the intersphincteric and transphincteric planes were defined with 1:300 000 adrenaline in saline solution. A circumferential incision was made on the lateral side of the anus in the intersphincteric groove. The intersphincteric plane was developed for the whole length of the anal canal. Superficial dissection was carried laterally and upwards into the ischiorectal fossa until the whole length of the external sphincter and puborectalis were defined A curved artery forceps was passed over the puborectalis, care being taken to ensure that all the puborectalis muscle was included. The puborectalis and upper half of the external sphincter were then divided with a scalpel cutting onto the artery forceps and the muscle ends were seen to retract. The skin wound was closed with 3/0 chromic catgut.

Since the initial results were disappointing, it was decided to produce further relaxation of the muscle by carrying out the procedure bilaterally, initially sequentially but later at the same procedure.

Twelve patients had a unilateral division performed, including three who had the operation performed on the same side twice. Three patients had a division performed on each side at two separate operations, and a further three patients had bilateral divisions performed at one operation.

Results (*Table 1*)

The mean follow-up was 13·5 months (range 4–24 months).

Symptomatic improvement

Only four patients noted subjective improvement in their symptoms, usually an increased sense of well-being and a decreased need to strain at stool. Three of these were patients with idiopathic constipation and one had a megarectum. Three of these patients had a bilateral division, while one had a unilateral division. Two of the patients had increased bowel frequency postoperatively. Symptomatic improvement showed some correlation with functional testing – none of these patients could expel a balloon pre-operatively while two could postoperatively. All four of these patients demonstrated electromyographic 'paradox' pre-operatively and this was still present postoperatively in three.

The mean bowel frequency of the entire group of patients was unchanged by the operation. Out of 14 patients who used laxatives pre-operatively, two who were symptomatically improved ceased using them postoperatively. One patient developed diarrhoea 6 months after the operation, and this was attributed to the previous colectomy.

Continence

Four patients had slight incontinence following the operation. This involved incontinence of mucus or infrequent urge incontinence; no patient had major faecal soiling. Of these four patients, two had a bilateral division and two had a unilateral division.

Balloon expulsion

Only one patient was able to expel the balloon pre-operatively, but six were able to do so postoperatively. Two of these six experienced symptomatic improvement.

Electromyography

This was measured pre- and postoperatively in 16 patients, all of whom demonstrated either no change in puborectalis muscle activity with straining or inappropriate contraction, rather than the normal relaxation. Four patients demonstrated appropriate relaxation postoperatively, of whom only one experienced symptomatic improvement (this patient was also able to expel a balloon postoperatively).

Anal manometry

The mean pre-operative (87±32 (s.d.) cmH_2O) and postoperative (95±35 cmH_2O) resting anal canal pressures were not significantly different. All patients demonstrated a fall in the maximum voluntary contraction pressure. The mean maximum voluntary contraction pressure, measured as the increment above resting pressure, was significantly reduced by the operation from 90±49 cmH_2O pre-operatively to 40±29 cmH_2O postoperatively ($P<0·0001$, Student's *t* test).

Discussion

Patients with severe constipation, either of the idiopathic type with a normal diameter rectum, or when the rectum is enlarged, often demonstrate paradoxical contraction of the pelvic floor striated musculature during defaecation straining[4–6]. An inability to evacuate the rectum, which can be simulated by failure to expel a water-filled balloon, has been attributed to this abnormal muscle activity 'blocking' the movement of rectal contents[5,6].

Although early reports on posterior division or resection of the puborectalis muscle were favourable[10,11], the patients appeared to be heterogeneous and had not been studied using electromyographic or other physiological techniques. Subsequent experience with posterior division in patients with severe idiopathic constipation who demonstrated pelvic floor abnormalities has been disappointing[7,12]. This poor result might have been due to persistence of external sphincter muscle activity, or perhaps due to extensive lateral attachment of the puborectalis muscle to the rectal wall. For these reasons, plus the fact that lateral internal sphincterotomy appears more efficacious than posterior sphincterotomy in the treatment of chronic anal fissures[8], we decided to perform lateral division of the puborectalis muscle and upper half of the external sphincter.

The criteria for the success or failure of this operation depended on the patient's opinion of the result. It was often hard to define whether this was more influenced by infrequent bowel actions, the need to strain, or the need to take laxatives. Detailed questioning showed no consistent pattern in this regard.

Only four of 18 patients expressed satisfaction with the results of the operation. In these four patients, improvement correlated with a newly acquired ability to expel a balloon from the rectum in two cases. In two of these four improved patients the bowel frequency was increased, and in the other two the need to strain at stool was reduced. Conversely, four other patients developed an ability to expel a water-filled balloon without symptomatic improvement. Three of the four improved patients were among the six who had bilateral divisions. It is perhaps not surprising that there was no consistent change in paradoxical contraction of the puborectalis as the operation was designed to weaken the muscle but not alter its function.

The evidence for the aetiological importance of abnormal pelvic floor activity in constipation is contradictory. The lack of improvement in these patients occurred despite a significant decrease in the maximum anal contraction pressure following surgery. Paradoxical pelvic floor contraction has been observed in patients with other anorectal disorders unaccompanied by constipation, and even some normal subjects[13]. Some constipated patients are unable to evacuate a balloon from the rectum, despite appropriate pelvic floor relaxation. The anorectal angle, observed during evacuation proctography and thought to relate to puborectalis activity, has also been studied in patients with severe constipation[14]: no significant difference has been found between controls and patients in the anorectal angle at rest or during evacuation. The inability to expel a balloon, contrast medium or saline from the rectum may be a reflection of an inability to co-ordinate rectal expulsion, independent of puborectalis and external sphincter function. On the other hand, biofeedback conditioning aimed at pelvic floor relaxation has been used successfully to treat patients with severe constipation[15].

The ability to expel a balloon from the rectum should be regarded as a useful test in severe constipation, but one whose mechanism is different from normal defaecation. Similarly, electromyographic abnormalities of the pelvic floor are common in severe constipation, but may not be aetiologically important. In this study, and in a study of pelvic floor abnormalities in patients undergoing total colectomy for severe constipation[16], these tests have proved to be of limited usefulness in selecting patients for a particular operation or predicting the outcome of surgery.

Many of the patients included in this study had slow intestinal transit. In most, the accumulation of radio-opaque shapes occurred in the left colon or rectosigmoid. Some groups have attributed this left-sided accumulation of shapes to outlet obstruction[17,18], but there is increasing evidence that a colonic disorder is also present. Silver staining of the colonic myenteric plexus in resected specimens from these patients shows morphological changes[19]. Dynamic studies in which the right colon is stimulated and transit monitored using radioisotope show abnormal motor response in severely constipated patients[20].

The surgical treatment of severe constipation remains controversial. Colectomy with ileorectal anastomosis is accompanied by considerable side-effects, with many patients experiencing diarrhoea, recurrent constipation or persistent abdominal pain[16]. Anorectal myectomy may be useful in some patients[17,21], but the selection criteria are not well established. Improved surgical therapy of these conditions in the future will depend on a greater understanding of the physiological abnormality, in particular the contribution of any colonic, rectal and anal disorder.

References

1. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation' *Gut* 1986, **27**: 41–8
2. Preston DM, Lennard-Jones JE, Thomas BM. The balloon proctogram. *Br J Surg* 1984; **71**: 29–32.
3. Barnes PRH, Lennard-Jones JE. Balloon expulsion from the rectum in constipation of different types. *Gut* 1985; **26**: 1049–52
4. Turnbull GK, Lennard-Jones JE, Bartram CI. Failure of rectal expulsion as a cause of constipation: why fibre and laxatives sometimes fail. *Lancet* 1986; **i**: 767–9.
5. Read NW, Timms JM, Barfield LJ, Donnelly TC, Bannister JJ Impairment of defaecation in young women with severe constipation. *Gastroenterology* 1986; **90**: 53–60.
6. Preston DM, Lennard-Jones JE. Anismus in chronic constipation. *Digest Dis Sci.* 1985; **30**· 413–18.
7. Barnes PRH, Hawley PR, Preston DM, Lennard-Jones JE. Experience of posterior division of the puborectalis muscle in the management of chronic constipation. *Br J Surg* 1985, **72**: 475–7.
8. Hawley PR. The treatment of chronic fissure-in-ano. *Br J Surg* 1969; **56**: 915
9. Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transit times using radio-opaque markers. *Gut* 1969; **10**: 842–7.
10. Wasserman IF. Puborectalis syndrome (rectal stenosis due to anorectal spasm). *Dis Colon Rectum* 1964; **7**: 87–98.
11. Wallace WC, Madden WM. Experience with partial resection of the puborectalis muscle *Dis Colon Rectum* 1969; **12**: 196–200.
12. Keighley MRB. Shouler P. Outlet syndrome: is there a surgical option? *J R Soc Med* 1984; **77**: 559–63.
13. Jones PN, Lubowski DZ, Henry MM, Swash M. Is paradoxical contraction of puborectalis muscle of functional importance? *Dis Colon Rectum* 1987; **30**: 667–70.
14. Turnbull GK, Bartram CI, Lennard-Jones JE. Radiological studies of rectal evacuation in adults with idiopathic constipation. *Dis Colon Rectum* 1988; **31**: 190.
15. Bleijenberg G, Kuijpers HC. Treatment of the spastic pelvic floor syndrome with biofeedback *Dis Colon Rectum* 1987, **30**: 108–11
16. Kamm MA, Hawley PR, Lennard-Jones JE. Is colectomy for severe idiopathic constipation a success? *Gut* 1987; **28**: A1343
17. Martelli H, Devroede G, Arhan P, Duguay C. Mechanisms of idiopathic constipation. outlet obstruction. *Gastroenterology* 1978; **75**. 623–31.
18. Beck DE, Jagelman DG, Fazio VW The surgery of idiopathic constipation. *Gastroenterol Clin N Am* 1987, **16**: 143–56.
19. Krishnamurthy S, Schuffler MD, Rohrmann CA, Pope CE II. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. *Gastroenterology* 1985; **88**: 26–34
20. Kamm MA, Thompson DG, Lennard-Jones JE *et al.* Dynamic colonic scanning – defining the regional defect in severe idiopathic constipation *Gut* 1987; **28**: A1365.
21. Yoshioka K, Keighley MRB. Anorectal myectomy for outlet obstruction. *Br J Surg* 1987; **74**: 373–6.

Paper accepted 26 February 1988

Br. J. Surg. 1988, Vol. 75, July,
664–667

The task of a statistical referee

G. D. Murray

Department of Surgery, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, UK
Correspondence to: Dr G. D. Murray

The results are presented of an audit of the statistical standard of papers published in The British Journal of Surgery. *A number of deficiencies are highlighted, many of which stem from an over-emphasis on statistical significance at the expense of any assessment of the clinical relevance of research findings. The flaws in the design of published studies, and in particular the many instances of inadequate sample sizes, emphasize that statistical input should be sought at the beginning of a research project rather than at the end.*

Keywords: Surgical studies, statistics, audit

In recent years there has been increasing recognition of the need to improve the standard of statistical methodology used in medical research. A number of reviews of leading medical journals[1–4] have shown a consistent pattern, with some 50 per cent of published papers containing identifiable statistical errors, of which around 50 per cent are classified as 'serious'.

The implications of inadequate statistical analysis are enormous, with some treatments erroneously being 'proved' to be effective, and with other promising treatments being written off early in their development. Altman[5] even argues that the widespread abuse of statistical methodology is a serious ethical issue: with subjects being put at risk or inconvenienced for no benefit, with resources having been diverted from more worthwhile use, with patients subsequently receiving an inferior treatment, and entire future paths of research being misdirected.

Many journals have responded to such reports by recruiting statistical referees, and before the adoption of such a policy, the Editorial Committee of *The British Journal of Surgery* commissioned an audit of the statistical standard of papers published in the Journal. This paper is based upon the findings of that audit and, as well as highlighting common statistical problems, it attempts to offer advice on how to avoid the pitfalls.

The audit was based upon three consecutive issues of the Journal, namely January to March 1987. In these issues I identified a total of 28 papers which made use of formal statistical methods, and I read each of these papers as if I were refereeing a manuscript submitted for publication. This review uncovered a large number of statistical flaws, which have been grouped together under the broad headings of design, presentation, analysis and interpretation.

Problems of design

It is at the design stage that a statistician has the greatest potential to contribute to the ultimate success of a research project. In my own experience, and in that of many of my statistical colleagues, it happens all too rarely that statistical advice is sought at this stage. Rather it is more common to be approached by an investigator who has completed a large data collection exercise, and who is seeking a liberal sprinkling of *P* values to render the study suitable for publication. Indeed the first contact is often made after the paper is returned by a journal with various statistical criticisms, and the statistician is expected to perform a salvage job on a study which more likely than not suffers from a fundamental design problem which not even the most sophisticated of analyses can overcome.

In fairness to investigators I should also point out that I have spoken to many clinicians who have consulted a statistician for advice and who have found the experience less than enlightening. Statisticians are very conscious of the difficulty of communicating statistical ideas to workers in other disciplines, and when approached 'cold' about a problem in a field about which the statistician has no background knowledge it is unrealistic to expect him to be able to offer appropriate advice. Rather, for a clinical research group undertaking a substantial programme of research it would be more appropriate to take a longer term view and to seek to develop a working relationship with a statistician who is prepared both to take an interest in their field and also to make the effort to understand the background and terminology of the area. It is far more stimulating for the statistician to be involved at this level, and provides an opportunity to give constructive advice.

The aims of the study

Usually the first role of the statistician is to force the investigator to specify the exact aim of the project. It is surprising that projects reach the stage of being published, yet the question being addressed is unclear. A basic principle of statistics is that one should design an experiment to test a single pre-specified hypothesis, and much of the controversy which surrounds the publication of major trials stems from the difficulty of interpreting the results of multiple *post hoc* analyses. To take too extreme a stand on this point is to deny the vital role which serendipity has played throughout the history of medical research, but it must be recognized that there are different degrees of quality of evidence. A single test of a pre-specified hypothesis carries far more weight than an 'interesting' *post hoc* subgroup analysis.

One can point to examples of this problem in most medical journals, but examples from the issues of *The British Journal of Surgery* which I reviewed can be found in Francis and Judson[6] and Terry *et al.*[7]. Both of these papers present the results of a large number of significance tests, and it is difficult to extract a clear message from either paper.

The size of the study

Once an investigator has specified the main question to be addressed it is possible for the statistician to advise on the size of study required. The approach is rather convoluted but, given a hypothesized treatment benefit, it is possible to determine how many subjects should be studied to have a certain probability (say 80 per cent) of the study being significant at a specified level (say $P < 0.05$), if the hypothesized treatment benefit actually exists. The results of these calculations can be surprising,

0007–1323/88/070664–04$3 00

especially if the study endpoint is a discrete event such as death, or the development of a deep vein thrombosis (DVT). For example, if one was investigating a prophylactic therapy which was intended to reduce the incidence of DVT in a group of patients where it was known that without prophylaxis the incidence was around 20 per cent, then one might hypothesize reducing this to 10 per cent. To be 80 per cent certain of being able to demonstrate this difference by achieving $P < 0{\cdot}05$, should such a treatment benefit indeed exist, a study of two groups of 200 patients, i.e. a total of 400 patients would be required. With this number of patients being required to demonstrate a strikingly effective treatment which prevents one DVT in two, it can be seen that an enormous study would be required to demonstrate smaller reductions, say from 20 per cent to 15 per cent, which could still be of great clinical relevance. Such arguments are a powerful counter to the attitude that 'if I cannot demonstrate a clear benefit in my study of 50 patients then the benefit must be so small as to be of no importance'.

From such considerations it can be seen that many of the small studies of rare complications which are frequently undertaken by surgeons (and others!) are essentially a waste of time. They will almost inevitably fail to show a 'significant' benefit and, worse, they tend to be reported as 'proving' a lack of efficacy whereas in fact they could easily conceal differences of enormous clinical relevance.

The calculations performed to estimate the required sample size for a study are known as power calculations, the power being the probability of the result being significant should the postulated treatment difference indeed exist. It was disappointing to find that not one of the studies in the three issues of *The British Journal of Surgery* which I reviewed made any reference to a power calculation, and there were numerous examples of studies where the sample size was so small that in effect they conveyed no information. For example, Dixon *et al.*[8] presented a survival curve based on 15 patients, only 3 of whom died during the study, and Francis and Judson[6] presented the results of a study of recurrence in 87 patients with colonic or rectal cancer. Only 28 recurrences were observed during the study, and by the time the patients were divided into subgroups on the basis of stage and tumour location, the groups were far too small to allow useful conclusions to be drawn.

In part this problem stems from an over-emphasis on the use of *P* values. Given only the *P* value from a negative study there is no way of distinguishing between a large, powerful study which demonstrates that two treatments are effectively equivalent, and a small study which is negative through lack of data. A far superior method of presenting the results of a study, and especially a negative study, is to use confidence intervals[9,10]. The *British Medical Journal* in particular has given a lead by insisting that confidence intervals should always be presented where they are appropriate[11], and a number of other journals are beginning to follow this lead.

The control of bias

A fundamental aspect of design is the control of bias. In comparing the outcome of two treatment groups one faces two sources of error. The first source is random variability and arises from the fact that only a finite number of subjects can be studied. If a study was repeated under 'identical conditions' then the results obtained would not agree exactly with those of the first study. This in theory (if not in practice) is not a serious problem, because the error can be quantified – indeed this is precisely what a significance test or confidence interval is doing – and moreover the error can be reduced to any desired level by the simple(!) expedient of recruiting sufficient subjects. A second source of error in a comparison is bias, which stems from systematic differences between the study groups. This is potentially far more serious than random variability in that it cannot be quantified and is not reduced by increasing the size of a study.

An example of such a bias occurs in Kissen and Kark[12]. In a study of nipple preservation during mastectomy, the authors studied prospectively 60 consecutive women undergoing mastectomy. Twenty women had their nipple preserved, and these women were compared with the 40 women in whom the nipple was removed. The aim was to compare recurrence rates, but it is impossible to infer from such a study that nipple preservation does not carry an excess risk of recurrence. The reason is that the indications for nipple preservation (small tumour, etc.) were themselves markers of good prognosis, and so there were systematic differences between the study groups. The number of recurrences was too small to draw any firm conclusions, but if anything I would take the fact that the recurrence rate in the nipple preserved group was similar to that in the other group as evidence that nipple preservation did carry an increased risk of recurrence in what should be a good prognosis group.

A more subtle example of such a bias occurs in Dowle *et al.*[13], where the authors examined the effects of introducing a breast self-examination education programme. In their *Figure 1* they compared the time from diagnosis to death in a group of 319 women diagnosed before the introduction of the programme with a group of 319 women diagnosed subsequently. One of several problems with this comparison was that the entire point of the programme was to allow early diagnosis, and so any benefit seen in terms of a prolongation of the time from diagnosis to death could be explained entirely by the effect of making earlier diagnoses. It is impossible with such an approach to establish a benefit in terms of survival following the development of the disease, which is what actually matters. Indeed being the Devil's advocate, one could even foresee a situation where the programme by leading to earlier diagnosis would allow an early and harmful intervention by the clinicians, hastening the woman's death but prolonging the time from diagnosis to death. The authors' analysis would 'prove' the efficacy of such an approach!

The single most useful tool which statisticians have devised for controlling bias is randomization. Properly executed, this procedure generates two study groups which only differ through random variability, and as long as no bias is then introduced related to the administration of the treatment and the assessment of response to treatment, a randomized controlled trial can yield very convincing evidence on the relative merits of two competing treatments. One point to be aware of, however, is the fact that some statisticians have defended randomization so vigorously that it has rather taken on an aura which gives respectability to poorly designed, poorly executed and poorly analysed studies, just because they are randomized. There is ample scope for bias in randomized studies as well as non-randomized studies, and this is another area where the advice of an experienced statistician can be invaluable.

Problems of presentation

Presentation can be broken down in turn into two areas: presentation of data and presentation of the results of a statistical analysis. Given unlimited journal space, the best way to present data is through a well chosen graphical display, and in general I thought that articles in the *British Journal of Surgery* made excellent use of such displays. Giving numerical summaries of data can be more difficult, and the usual practice is to present means and standard deviations for everything in sight. The mean and, in particular, the standard deviation, are only useful summaries when the data are symmetrically distributed. Many variables encountered in medicine are skewed, with all of the 'abnormal' values lying to one side of the distribution. For example, in the article by Horgan *et al.*[14], *Figure 2* clearly shows that means and s.e.m.s are not appropriate summary statistics. With such data it is far better to quote the median and the range or interquartile range.

A related point is that s.d. and s.e.m. are often confused, or else no explanation is given as to which is being used. Simpson *et al.*[15], for example, stated that *Table 1* gives s.d.s. but almost certainly they are s.e.m.s, and Harju and Isolauri[16] gave no indication of what is meant by the ubiquitous '±' symbol. Here again the *British Medical Journal* has given a lead[17] in discouraging use of the '±' symbol and suggesting instead that means should be presented as '14·2 (s.e.m. 1·9)' or '14·2 (s.d. 7·4)'.

In presenting derived quantities such as means and s.d.s there is a tendency to quote more significant figures than is justified. Whether this is unthinking or is to give a spurious impression of precision is unclear, but in Kissen and Kark[12] we are told that the mean tumour diameter was 39·88 mm, and Dennison *et al.*[18] report $t = 9{\cdot}2248$, $P >$ (sic) 0·0001, when all that really matters is the fact that the t statistic exceeds 2!

In presenting the results of an analysis there was a very marked tendency to quote P values as if they were descriptive statistics. Many of the summaries in particular quote only P values. In Dowle *et al*[13] the most interesting finding is reported as 'there has been a significant reduction in the size at presentation of operable tumours ($P < 0{\cdot}01$)'. 'So what?' one might well respond. It would be far better to know that there was (say) a 28 per cent reduction, and the significance or otherwise of this finding could be conveyed via a confidence interval. In general the advice is very simple—describe the results in terms of a number which has a clear clinical interpretation rather than a P value which in isolation is meaningless.

Problems of analysis

As is common in all such reviews of medical journals, there were many examples of inappropriate statistical analyses. Often the problem was simply that the methods were not described adequately[16,18,19], which makes it rather difficult to assess their validity! Indeed Simpson *et al.*[15] claim $P < 0{\cdot}05$ without even presenting the data or the statistical methods used.

At a fairly basic level there were examples of simple computational errors and there were also examples of inappropriate tests with, for example, t tests being used where the distributions were very skewed or where the standard deviations of the two groups differed substantially[7].

A more subtle but far more serious error is to treat related measurements as if they are independent. Matthews *et al.*[20] for example analysed proliferation indices derived from tissue samples, but in several cases more than one sample was taken from the same individual. Such data require very sophisticated analysis, and to apply a Mann–Whitney test as was done is a very serious error which can generate spuriously significant findings.

Another common problem is the (mis)use of multiple tests. This can arise in many ways, including when more than two treatment groups are studied[21], when more than one endpoint is analysed[22], when subgroups are compared[6], and where the same measurements are made repeatedly through time on the same individuals[23,24]. For each of these situations there is appropriate statistical methodology which can be applied, but these methods were almost totally ignored in the articles reviewed. Their neglect is again a serious problem because to fail to adjust for the multiple comparisons generates spuriously significant results. It is beyond the scope of this article to describe valid methods of analysing such data, but it is worth pointing out that the key to success is to have, *a priori*, a very clear idea of the aim(s) of the study, and, of course, to enlist statistical help at an early stage.

Problems of interpretation

Clearly all of the problems discussed so far can result in misleading conclusions being drawn from a study. But even when there are no problems of design or analysis there is still scope to draw erroneous conclusions. Largely these problems stem from an over-emphasis on P values, when instead there should be more emphasis on estimation and on describing results in terms of immediate clinical relevance.

The most common error is to regard a non-significant result as proving that two groups are identical. This is not the correct interpretation of a negative finding, which corresponds to the Scottish legal verdict of not proven. One example from the many which I could have given occurs in Kairaluoma *et al.*[25] where two 5-year survival rates were compared, and since there is no significant difference it is concluded that the rates are indeed equal. However, the rates being compared were 25 per cent and 58 per cent respectively, and the non-significant result merely highlighted the inadequate sample size. Clearly there might be no difference or there might be an enormous difference, and the data were insufficient to distinguish between these possibilities. If the results had been presented using a confidence interval then it would have been clear that the data were inadequate, and the error of interpretation could have been avoided.

Although less common, it is possible for a significant result to be interpreted erroneously as being clinically relevant. This can happen in screening studies where, because of the enormous sample sizes employed, very small differences of no clinical relevance can be statistically significant. Some of the results of Leinster *et al.*[26] are heading in this direction, with rather modest differences being highly significant statistically.

A more serious error in the interpretation of a significant finding can occur in the assessment of diagnostic or screening procedures. Matthews *et al.*[20] demonstrated significant differences in the median 'proliferation index' between control patients and patients with neoplasms, but the populations overlapped to such an extent that the index would have little diagnostic value. The vast majority of the patients' proliferation indices lay within the normal range of the control patients.

Discussion

It is difficult to give an objective assessment of the validity of a statistical analysis. Rather like medicine, statistics is an art, and there is rarely a unique correct approach. Rather judgement is necessary to select one of a number of possible analyses, each with their own advantages and limitations. In my review I encountered many analyses which I would have tackled differently, but where in my judgement the analysis as presented was perfectly acceptable. In writing this article I have attempted to confine my criticisms to points where I believe that the vast majority of statisticians would agree that the approach adopted was not acceptable, and indeed many statisticians would probably take a harder line than I have. My statistical philosophy leans towards being a realist rather than a purist, and my research interests lie in the area of how to obtain the least biased results possible in areas where perhaps for ethical or practical reasons randomization is not possible, or where missing data abound.

As an indication of how serious I consider the errors encountered in reviewing the three issues of *The British Journal of Surgery*, I took my refereeing exercise to its logical conclusion and made recommendations on their suitability for publication. Of the 28 papers reviewed, I would have rejected 4 (14 per cent) outright and for a further 7 (25 per cent) my recommendation would have been that the authors were invited to resubmit their manuscripts after substantial revision of the statistical analyses. Eleven (39 per cent) others I would have accepted subject to minor cosmetic alterations, many of which could have been made at the editing stage, and there were only 6 (21 per cent) which I considered to need no modification. This of course, is a retrospective, uncontrolled, and highly subjective study; which by my own criteria I would probably reject outright! However, I do believe that it deserves careful consideration.

References

1 Schor S, Karten I. Statistical evaluation of medical journal manuscripts. *JAMA* 1966; **195**: 1123–6.

2. Gore SM, Jones IG, Rytter EC. Misuse of statistical methods: critical assessment of articles in *BMJ* from January to March 1976. *Br Med J* 1977; i. 85–7.
3. White SJ. Statistical errors in papers in the *British Journal of Psychiatry*. *Br J Psychiatry* 1979; **135**: 336–42.
4. Pocock SJ, Hughes MD, Lee RJ Statistical problems in the reporting of clinical trials: a survey of three medical journals *N Engl J Med* 1987; **317**, 426–32.
5. Altman DG. Statistics in medical journals. *Statistics in Medicine* 1982; **1** 59–71.
6. Francis DMA, Judson RT. Blood transfusion and recurrence of cancer of the colon and rectum *Br J Surg* 1987, **74**: 26–30.
7. Terry TR, Grant DAW, Hermon-Taylor J. Intraduct enterokinase is lethal in rats with experimental bile-salt pancreatitis. *Br J Surg* 1987; **74**: 40–43
8. Dixon JM, Lumsden AB, Krajewski A, Elton RA, Anderson TJ Primary lymphoma of the breast. *Br J Surg* 1987; **74**: 214–7.
9. Gardner MJ, Altman DG Confidence intervals rather than *P* values: estimation rather than hypothesis testing. *Br Med J* 1986; **292**: 746–50.
10. Bulpitt CJ. Confidence intervals. *Lancet* 1987, **i**: 494–7.
11. Langman MJS. Towards estimation and confidence intervals *Br Med J* 1986; **292**: 716.
12. Kissen MW, Kark AE Nipple preservation during mastectomy. *Br J Surg* 1987; **74**: 58–61
13. Dowle CS, Mitchell A, Elston CW *et al* Preliminary results of the Nottingham breast self-examination education programme. *Br J Surg* 1987; **74**: 217–9.
14. Horgan K, Jones DL, Mansel RE Mitogenicity of human fibroblasts *in vivo* for human breast cancer cells *Br J Surg* 1987, **74**: 227–9.
15. Simpson CJ, Lamont G, Macdonald I, Smith IS. Effect of cimetidine on prognosis after simple closure of perforated duodenal ulcer. *Br J Surg* 1987, **74**: 104–5.
16. Harju E, Isolauri J. Dietary habits of patients with regurgitation after colon interposition. *Br J Surg* 1987; **74**: 169–71
17. Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J* 1983, **286**: 1489–93.
18. Dennison AR, Collin J, Watkins RM, Millard PR, Morris PJ. Absorptive and motor function of orthotopically vascularized segmental ileal autografts *Br J Surg* 1987; **74**: 187–91.
19. Schweizer W, Stahel E, Betschart B *et al*. Chloroquine administration for malaria suppression after abdominal surgery. *Br J Surg* 1987; **74**: 140–1
20. Matthews JL, Glynn M, Parkins A, Cooke T. Alteration in colonic epithelial cell DNA associated with intestinal neoplasia: selection of high risk patients. *Br J Surg* 1987; **74**: 23–5.
21. Frizis HI, Whitfield PF, Hobsley M. Maximal gastric secretion and duodenogastric reflux in patients with gastric or duodenal ulcer and in control subjects *Br J Surg* 1987; **74**: 106–9.
22. McEntee GP, McPhail S, Mulvin D, Thomson RW. Single dose antibiotic prophylaxis in high risk patients undergoing transurethral prostatectomy. *Br J Surg* 1987; **74**: 192–4.
23. Ross WB, Tweedie JH, Leong YP, Wyman A, Smithers, BM Does intercostal blockade improve patient comfort after cholecystectomy? *Br J Surg* 1987, **74**: 63.
24. Kang JH, Kambayashi J, Sakon M *et al* Mechanism of the haemostatic effect of ethanolamine oleate in the injection sclerotherapy for oesophageal varices. *Br J Surg* 1987, **74** 50–3.
25. Kairaluoma MI, Kiviniemi H, Stahlberg, M Pancreatic resection for carcinoma of the pancreas and the periampullary region in patients over 70 years of age. *Br J Surg* 1987; **74**: 116–8.
26. Leinster SJ, Whitehouse GH, Walsh PV Cyclical mastalgia: clinical and mammographic observations in a screened population. *Br J Surg* 1987; **74**: 220–2.

Paper accepted 2 March 1988

This review was commissioned as part of our own continuing critical assessment of *The British Journal of Surgery*. Although the views expressed here are personal we feel that the review has produced findings of sufficient interest to merit publication.

The Editors

Br. J. Surg. 1988, Vol. 75, July, 668–670

Intravenous digital subtraction angiography and Duplex scanning in the detection of late human umbilical vein degeneration*

A. Nevelsteen, G. Smet, G. Wilms†, G. Marchal† and R. Suy

Departments of Cardiovascular Surgery and †Radiology, University Clinic Gasthuisberg, Leuven, Belgium

Correspondence to:
Dr A. Nevelsteen

To define the exact incidence of late degeneration, 32 patients underwent intravenous digital subtraction angiography (IVDSA) and/or a Duplex scan more than 3 years after human umbilical vein (HUV) grafting. IVDSA (n = *26) showed a 23 per cent aneurysmal degeneration rate which increased to 40 per cent with Duplex scanning* (n = *25). Although the differences obtained in those patients receiving both examinations* (n = *19) were statistically not significant, Duplex scanning appeared to be more sensitive, demonstrating two additional cases of aneurysmal degeneration not detected by IVDSA. Since, moreover, Duplex scanning proved able to detect anastomotic stenosis, it appears to be the examination of choice in long-term follow-up of the HUV graft. Despite this relatively high degeneration rate, the authors consider continued use of the HUV graft in selected patients to be justified, especially when the long-term patency rates, the available alternatives, and the less favourable long-term survival after femoropopliteal reconstruction are taken into consideration.*

Keywords: Femoropopliteal reconstruction, aneurysm, angiography, arterial prosthesis, Duplex scan, atherosclerosis

Soon after its introduction in 1975, the human umbilical vein (HUV) graft (Biograft®, Meadox Medicals Inc., Oakland, New Jersey, USA) became one of the most popular prostheses for lower limb revascularization. Acceptable patency rates have been reported by several authors[1–4]. Although this biological graft was protected with a Dacron (E I. Dupont de Nemour Inc.) mesh, Giordano and Keshihian[5] reported the first cases of late aneurysm formation. Since then several reports have appeared, but the exact incidence and the relative value of angiography and Duplex scanning in detecting these complications are still under discussion. The purpose of this report is to define the exact incidence of aneurysmal degeneration and to compare the relative value of angiography and Duplex scanning during late follow-up of patients with HUV grafts.

Patients and methods

From 1978 until the end of 1986 the HUV graft was used in our department for 156 femoropopliteal and 48 femorotibial reconstructions. During follow-up, clinical examination revealed only four cases of aneurysmal degeneration, all occurring more than 3 years after graft implantation. However, all of the femoropopliteal and 62 per cent of the femorotibial grafts were placed in deep anatomical positions and were not readily available for clinical examination over their entire length. Moreover, after studying the reports of Hasson *et al* [6] and Karkow *et al* [7], the actual incidence of late degeneration was suspected to be much higher Therefore it was decided to re-evaluate all patients surviving with a patent graft for more than 3 years by means of intravenous digital subtraction angiography (IVDSA) and/or Duplex scanning. Of 44 patients available at the time of the study, 32 (73 per cent) agreed to co-operate. The mean follow-up of this series was 57·4 months (range 37–100 months) IVDSA was performed in 26 patients and Duplex scanning in 25 reconstructions; 19 patients received both examinations, allowing comparison of both methods.

Angiography and Duplex scanning were performed independently. Results were analysed in a blind fashion by two of the authors, taking only the most severe classification into consideration IVDSA studies were performed with Angiotron or Digitron equipment (Siemens, Erlangen, FRG). Injection of contrast medium was performed via a 5 French pigtail catheter advanced in the right atrium Angiographic changes were graded accordingly to Hasson *et al.*[6]:

0 = smooth luminal surface, no evidence of dilatation;
1 = minimal wall irregularity without dilatation;
2 = moderate wall irregularity, with dilatation and/or ulceration,
3 = fusiform dilatation/ectasia with saccular or fusiform aneurysms

For Duplex scanning the method described by Karkow *et al.*[7] was followed, using an Acuson 128 (Mountain View, California, USA) scanner with a 5 MHz linear probe and dividing the lower extremity into different zones. Here also a graft was considered aneurysmal if its lumen was equal to or greater than 9 mm and/or if the outer diameter was enlarged by 50 per cent (equal to or greater than 13·5 mm). Furthermore, degenerative changes were subdivided into localized midshaft aneurysms, diffuse aneurysmal dilatation or anastomotic aneurysms

Results

Duplex scanning was performed in 25 patients (mean follow-up 57·5 months; range 37–100 months) and aneurysmal changes were seen in 10 (40 per cent). Localized midshaft aneurysms were found in five grafts, three patients presented a diffuse aneurysmal dilatation in combination with localized aneurysms while anastomotic aneurysms were detected in another two reconstructions (*Figure 1*). Multiple aneurysms were seen in four grafts with a maximum of five aneurysms in one graft 4 years postoperatively. For a total of 16 midshaft aneurysms, 12 were of the fusiform and 4 of the saccular type. The outer diameter of the aneurysms ranged from 14·2 mm to 27·8 mm with a mean of 18 mm. Apart from these degenerative changes, Duplex scanning also showed a significant anastomotic stenosis in three patients (12 per cent).

IVDSA performed in 26 patients (mean follow-up 58·7 months; range 37–100 months) showed frank aneurysmal degeneration in six reconstructions (23 per cent, *Figure 2*). The majority of the patients (50 per cent) presented with pre-aneurysmal (grade 2) changes, while only one graft proved to be completely normal (*Table 1*). Apart from an anastomotic aneurysm in one patient, an unsuspected anastomotic stenosis was found in four reconstructions (15 per cent).

---

* *This study was partially supported by NFWO grant No. 9 0015 85*

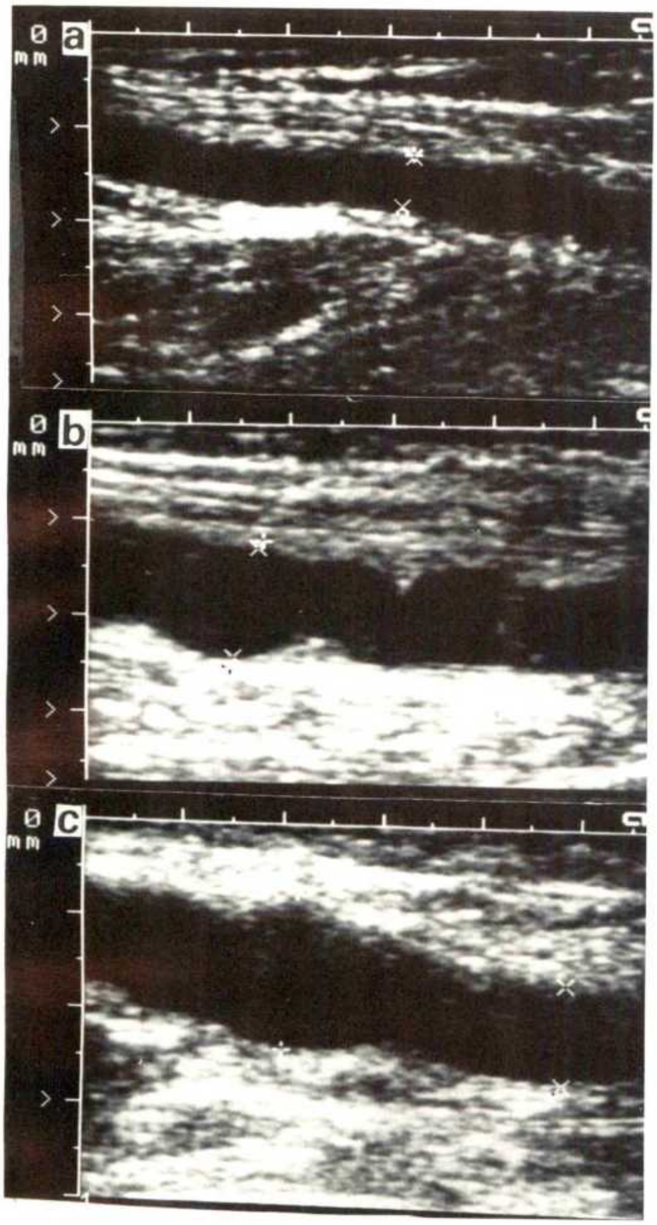


Figure 1 *Duplex scan of human umbilical vein graft with* **a** *normal appearance,* **b** *localized midshaft aneurysm,* **c** *diffuse aneurysmal dilatation*

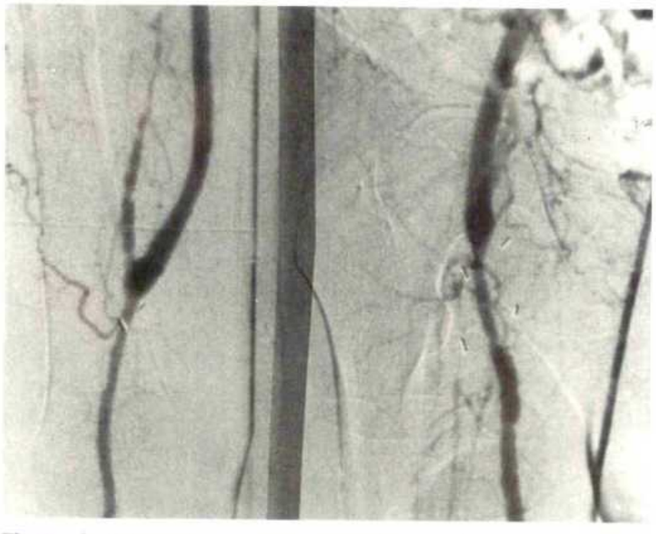


Figure 2 *Intravenous digital subtraction angiography 4 years postoperatively showing aneurysmal degeneration*

A comparison of angiography and Duplex scanning was possible in 19 patients (mean follow-up 59·9 months; range 37–100 months). As shown in *Table 2*, the results corresponded completely for those grafts angiographically classified as grade 0, 1 or 3. In two patients with grade 2 angiographic changes, Duplex scanning showed a more pronounced aneurysmal degeneration. However, it concerned aneurysms with an internal diameter of respectively 9·2 and 9·8 mm and the results obtained with angiography or Duplex scanning were not significantly different ($P = 0{\cdot}25$). Anastomotic stenosis, angiographically demonstrated in three patients of this series, was also confirmed in all cases by Duplex scanning (*Figure 3*).

Discussion

Biodegradation has been recognized for several decades as the *bête noire* of the long-term function of any arterial prosthesis of biological origin[8,9]. Aneurysm formation in the glutaraldehyde-stabilized HUV graft was first reported by Giordano and Keshihian[5]. Additional cases have been described[3,10–12], but the reported incidence has remained well below 5 per cent. However, it soon became apparent that these preliminary reports were too optimistic since, first of all, they all related the incidence of aneurysm formation to the total number of grafts inserted. By relating the number of aneurysms to the number of grafts at follow-up at different periods, the incidence already sharply increases to as much as 45 per cent in grafts still patent 4 years after implantation[7]. Secondly, most of the previous reports rely only on clinical signs, which are known to be poor discriminators for aneurysm detection. With clinical examination we were able to detect only four aneurysms in our series of 204 grafts, an incidence of 2 per cent, but this increased to 8·3 per cent when related to the number of grafts still patent after 3 years ($n = 48$).

In 1986, Boontje[13] published an angiographic follow-up study on 217 HUV grafts. He discovered diffuse or local signs of biodegradation in 46 per cent of the grafts still patent after 3 years. Later on, Hasson *et al.*[6] reported on a series of 14 HUV grafts implanted for more than 2 years with an angiographic aneurysmal degeneration rate of 57 per cent (so-called grade 3 changes). Pre-aneurysmal (grade 2) changes were seen in three grafts and by serial follow-up these authors were able to demonstrate progression from grade 2 to grade 3 in one patient. By IVDSA and with a minimum follow-up of 3 years, we only arrived at a 23 per cent incidence of frank aneurysmal degeneration. However, combining grade 2 and grade 3 changes, our 73 per cent incidence of biodegradation compares well with the 79 per cent reported by Hasson *et al.*[6]. It should be mentioned, however, that we only included those grafts still available for follow-up after 3 years.

Table 1 *Angiographic classification of changes* (n = *26*)

Angiographic grade	*n*
0	1 (4%)
1	6 (23%)
2	13 (50%)
3	6 (23%)

Table 2 *Comparison between angiography and Duplex scan* (n = *19*)

Angiography		Duplex scan	
Angiographic grade	*n*	Normal*	Aneurysmal changes
0	1	1	
1	4	4	
2	9	7	2
3	5		5

* No aneurysmal changes on Duplex scan

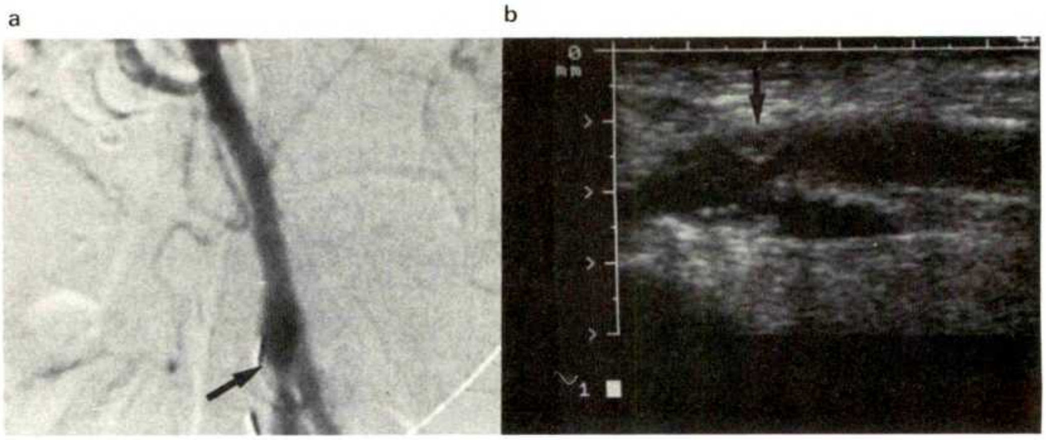


Figure 3 *Anastomotic stenosis, 39 months postoperatively, as demonstrated by* **a** *intravenous digital subtraction angiography and confirmed by* **b** *Duplex scanning*

Recently, Karkow *et al.*[7] described Duplex scanning of 64 HUV grafts. With a minimum follow-up of 3 years, they noted aneurysmal degeneration in 46·8 per cent of the cases. On theoretical grounds they also stated that Duplex scanning should be preferred to angiography for detecting aneurysmal degeneration. Although the differences were not statistically significant, Duplex scanning proved to be more accurate on two occasions in our series. Furthermore, aneurysm formation may angiographically be underestimated due to internal thrombus formation. Duplex scanning, on the other hand, provides the exact size of the aneurysm. Moreover, it is less invasive than IVDSA and its capability of detecting stenotic lesions makes it the preferred method of follow-up for patients with a HUV graft.

Although the presented and previously reported degeneration rates of the HUV graft seem dramatic, we feel that these results should be interpreted with care. The value of the graft has to be weighed against that of other available prostheses. As has been reported by others[7,10], patency rates achieved in our patients remain second only to those obtained with the saphenous vein. Secondly, due to late occlusion and patient mortality, in our series of 204 grafts less than 25 per cent survived at 3 years and only 11 per cent at 5 years or more. So, if biodegradation creates a problem, it will do so in only a small minority of patients. Thirdly, the importance of degenerative changes in long-term patency has not been established. On the contrary, continued patency has been reported in aneurysmal grafts and lesser degrees of degeneration do not seem to compromise long-term function[7,13]. In this series also, now with a mean follow-up of 6 months since IVDSA and including 16 aneurysms with a maximum size of 27·8 mm, we have seen no complications, although no operative procedures for degenerative disease have been performed. Finally it has been proved that most cases of late degeneration are due to insufficient strength of the surrounding Dacron mesh. Recently, the manufacturer has covered the graft with a new mesh which is 12 times stronger than the old. In combination with a modification of the tanning procedure it is hoped that resistance against degradation will improve. So, in conclusion, we feel that continued use of the HUV grafts is justified provided that these reconstructions are reserved for patients with advanced ischaemia and that regular control studies (preferably by Duplex scanning) can be performed.

References

1. Dardik H, Baier RE, Meenaghan M *et al.* Morphologic and biophysical assessment of long-term human umbilical cord implants used as vascular conduits. *Surg Gynecol Obstet* 1982; **154**: 17–26.
2. Raithel D, Schweiger H, Geutsch HH. Late results with Dardik-biograft in peripheral arterial surgery. *J Cardiovasc Surg* 1984; **25**: 222–4.
3. Hirsch SA, Jarrett F. The use of stabilized human umbilical vein for femoropopliteal bypass: experience with 133 operations with 5 year follow-up. *Ann Surg* 1984; **200**: 147–52.
4. Nevelsteen A, D'Hallewin MA, Deleersnijder J, Wouters L, Suy R. The human umbilical vein graft in below-knee femoropopliteal and femorotibial surgery: an eight year experience. *Ann Vasc Surg* 1986; **1**: 328–34.
5. Giordano JM, Keshihian JM. Aneurysm formation in human umbilical vein grafts. *Surgery* 1982; **91**: 343–5.
6. Hasson JE, Newton WD, Waltman AC *et al.* Mural degeneration in the glutaraldehyde-tanned umbilical vein graft: incidence and implications. *J Vasc Surg* 1986; **4**: 243–50.
7. Karkow WS, Cranley JJ, Cranley RD, Hafner CD, Ruoff BA. Extended study of aneurysm formation in human umbilical vein grafts. *J Vasc Surg* 1986; **4**: 486–92.
8. Keshihian JM. Experiences with use of bovine heterografts in the arterial position. In: Sawyer PM, Kaplitt MJ, eds. *Vascular Grafts*. New York: Appleton-Century-Crofts, 1978: 271–2.
9. Hallin RW, Sweetman WR. The Sparks' mandril graft. *Am J Surg* 1976; **132**: 221–3.
10. Jamieson CW. Umbilical vein for bypass operations. *Br Med J* 1983; **287**: 244–5.
11. Boontje AH. Aneurysm formation in human umbilical vein grafts used as arterial substitutes. *J Vasc Surg* 1985; **2**: 524–9.
12. Dardik H, Ibrahim IM, Sussman B *et al.* Biodegradation and aneurysm formation in umbilical vein grafts. Observations and a realistic strategy. *Ann Surg* 1984; **199**: 61–8.
13. Boontje AH. Angiographic assessment of Biografts for femoropopliteal bypass. *J Cardiovasc Surg* 1986; **27**: 136–40.
14. Eickhoff JH, Buchardt Hansen HJ, Bromme A *et al.* A randomized clinical trial of PTFE versus human umbilical vein for femoropopliteal bypass surgery. Preliminary results. *Br J Surg* 1983; **70**: 85–8.

Paper accepted 26 February 1988

Br. J. Surg. 1988, Vol. 75, July,
671–674

Effects of autologous mesothelial cell seeding on prostacyclin production within Dacron® arterial prostheses

H. A. Bull*, R. M. Pittilo†, J. Drury§, J. G. Pollock§, J. M. F. Clarke‡, N. Woolf†, A. Marston‡ and S. J. Machin*

*Departments of *Haematology, †Histopathology and ‡Surgical Studies, The Middlesex Hospital Medical School, London, and §Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK*

Correspondence to: Dr H. A. Bull, Department of Dermatology, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Canine abdominal aortas have been replaced with Dacron® arterial prostheses to assess the effects of mesothelial cell seeding on graft prostacyclin and thromboxane A_2 release. At both 2 weeks and 6 weeks after surgery, three seeded and two unseeded control grafts were examined for prostacyclin release. In addition, thromboxane release was assessed in one seeded and one unseeded graft. Sections of aorta and graft were removed and incubated in PBS containing either 10 μM calcium ionophore A23187 or 20 μM arachidonic acid. The incubation mixture was sub-sampled at 5 min intervals over a 20 min period to assess the progressive release of prostacyclin and thromboxane A_2 using a radioimmunoassay for 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 respectively. In seeded grafts, 6-keto-prostaglandin $F_{1\alpha}$ release averaged 15 per cent compared with aorta at 2 weeks and 45 per cent compared with aorta at 6 weeks. By contrast, release from unseeded grafts was undetectable at 2 weeks; however, by 6 weeks there was some release amounting to 15 per cent compared with aorta. There was a statistically significant increase in the release of 6-keto-prostaglandin $F_{1\alpha}$ from mesothelial cell seeded grafts at 6 weeks compared with unseeded grafts ($P<0{\cdot}01$). Thromboxane release from the graft sections was variable and unrelated to whether the grafts had been seeded or not. These preliminary results, showing that grafts seeded with autologous peritoneal mesothelial cells release more prostacyclin than unseeded grafts, further highlight the role of the mesothelial cell as an alternative to the endothelial cell for improving the patency of arterial Dacron prostheses in the early postoperative days.

Keywords: Mesothelium, prostacyclin, arterial prostheses

When Dacron prostheses are used in the reconstruction of small-bore vessels, failure frequently results because the luminal surface is thrombogenic. Thrombus formation and re-occlusion occur because, in man, arterial grafts do not become lined with endothelial cells[1]. Even if the graft survives the initial period of implantation and 'healing', failure can still result from additional factors such as atherosclerosis within the graft[2].

The technique of endothelial cell seeding of Dacron (E.I. Dupont de Nemour, Inc.) grafts before implantation, using cells from a variety of sources, has been extensively investigated and results in an enhanced endothelial lining[3,4]. However, as has been pointed out by Clarke *et al.*[5], although endothelial cell seeding represents a significant innovation, clinical application is difficult because autologous vascular endothelium is not readily available at the time of surgery.

More recently, attention has turned to the mesothelial cell as a possible alternative for seeding arterial prostheses. Visceral mesothelial cells have been shown to support blood flow[6]. Furthermore, mesothelial cells can easily be harvested from omental tissue and these cells, when cultured *in vitro*, support blood flow[7]. These studies demonstrate that the more readily available mesothelial cell holds promise as a substitute for endothelial cells, in the role of seeding arterial grafts. Further support for this concept was obtained in a study in dogs, in which the mesothelial cell seeding of Dacron grafts at the time of implantation resulted in significant coverage of the luminal surface by 4 weeks[5].

The non-thrombogenicity of the endothelium has been attributed in part to the fact that it releases prostacyclin (PGI_2), the most potent natural inhibitor of *in vitro* platelet aggregation yet isolated[8,9]. Mesothelial cells also release PGI_2 and there is evidence to suggest that, *in vitro* at least, they may produce more than endothelial cells[10].

Endothelium also releases small amounts of thromboxane A_2 (TXA_2)[11], which potentiates platelet aggregation and it has been reported that increased release of TXA_2 and decreased release of PGI_2 are associated with loss of endothelial thromboresistance[12].

The purpose of this paper is to report our preliminary findings on the effect of mesothelial cell seeding on PGI_2 and TXA_2 release by the pseudo-intima of arterial grafts.

Materials and methods

Surgery and graft seeding

The surgical procedure and mesothelial cell harvesting were carried out essentially as previously described[5,7]. The dogs were anaesthetized and intubated. The abdomen was opened and at this stage, in dogs receiving mesothelial cell-seeded grafts, a piece of omentum was removed and placed in 20 ml collagenase solution (0·5 per cent collagenase in phosphate buffered saline (PBS)). After 30 min incubation at 37°C, the tissue was removed from the collagenase solution. The cell suspension was pelleted by centrifugation at 1000 rev/min for 5 min and resuspended in PBS. This washing procedure was repeated twice; after the final centrifugation, the cells were resuspended in 2 ml PBS. Meanwhile, sections of Dacron tube

0007–1323/88/070671–04$3.00

(Vascutek Ltd, UK) were selected for pre-clotting. The prostheses were flushed with 10 ml autologous blood until it clotted. This process was repeated and in those dogs receiving seeded prostheses, the aliquots of blood contained 1 ml mesothelial cell suspension. Finally, both seeded and unseeded grafts were flushed with blood containing 10 000 units heparin. The grafts were inserted below the renal artery and above the bifurcation of the iliac arteries. Circulation was restored and the dogs were allowed to recover.

In this series of experiments, six mongrel dogs received Dacron arterial prostheses that had been seeded with mesothelial cells; a control group of four dogs received unseeded grafts. At both 2 weeks and 6 weeks postoperatively, three dogs with implanted seeded grafts and two control dogs were killed and samples of graft and adjacent aorta were taken to assess PGI_2 release. Thromboxane A_2 release was assessed in one seeded and one unseeded graft and adjacent aorta at 2 and 6 weeks after implantation. All the grafts used in these studies were patent at the time of removal from the animal.

Prostacyclin and thromboxane assays

Prostacyclin is an unstable arachidonic acid metabolite with a half-life of less than 12 min at pH 7·4. It is rapidly hydrolysed to form 6-keto-prostaglandin $F_{1\alpha}$ (6k-$PGF_{1\alpha}$), which is a relatively stable metabolite. Prostacyclin release has been assessed using a radioimmunoassay for 6k-$PGF_{1\alpha}$, as previously described[13].

Thromboxane A_2 is even less stable than prostacyclin, with a half-life of about 30 s at pH 7·4. It is rapidly converted into thromboxane B_2 and levels of this stable metabolite have been measured using a radioimmunoassay, to assess release of thromboxane A_2.

Sections from the mid-portion of the grafts and sections of aorta at least 2 cm from the anastomosis were removed as quickly as possible after exposure of the abdominal cavity. The sections were rinsed in warm PBS, trimmed of external tissue and cut open longitudinally. The sections were then placed in a fresh 3 ml aliquot of PBS containing either 10 μM calcium ionophore A23187 (Sigma) or 20 μM arachidonic acid (Sigma). The sections were incubated on a rocking platform and at 5, 10, 15 and 20 min, 150 μl aliquots were removed from the incubation mixture, placed on ice then frozen at −20°C for radioimmunoassay at a later date. After 20 min the sections were removed from the incubation buffer and blotted dry. They were then traced on to paper and the pieces of paper weighed. It was felt that weighing pieces of paper corresponding to the surface area of the section would overcome the differences in weights of identical-sized sections of aorta and graft. The 6k-$PGF_{1\alpha}$ and TXB_2 levels were expressed as ng/mg paper weight.

Statistical analysis

The mean release of 6k-$PGF_{1\alpha}$ from unseeded grafts was compared with that from mesothelial cell-seeded grafts using Student's *t* test. The release of 6k-$PGF_{1\alpha}$ after a 20 min incubation was compared in grafts implanted for 6 weeks. It was not possible to compare release of 6k-$PGF_{1\alpha}$ from grafts implanted for 2 weeks as there was no detectable release of 6k-$PGF_{1\alpha}$ from unseeded grafts.

Light microscopy

In order to ensure that the mesothelial cell-seeding procedure had been successful, sections of seeded graft, before insertion, were rinsed in warm PBS and then placed in an aliquot of glutaraldehyde fixative (2·5 per cent v/v glutaraldehyde in 0·1 M cacodylate buffer, pH 7·2). After an hour, the samples were cut open longitudinally and transferred to a fresh aliquot of glutaraldehyde fixative. They were then processed through alcohol and xylene and embedded in paraffin wax at 60°C; sections 4 μm thick were cut and mounted on glass slides. These were dewaxed and rehydrated before being stained with haematoxylin and eosin.

Results

Prostacyclin release

Under basal conditions, vascular tissue releases minimal amounts of prostacyclin. However, the actual process of removing the sections of aorta and graft from the animal is sufficiently traumatic to induce some release of prostacyclin. In order to maximize the prostacyclin release during the *ex vivo* incubation period, the sections were incubated in the presence of either arachidonic acid (the prostacyclin precursor) or the calcium ionophore A23187 (a known stimulator of prostacyclin release)[14]. Stimulation of PGI_2 release was not significantly different in the presence of either agonist and so the data from the two groups were combined.

Levels of 6k-$PGF_{1\alpha}$ released from the sections of aorta and graft are shown in *Figure 1*. After 20 min, release from the sections of aorta averaged 8·25 ± 0·77 ng/mg. In seeded grafts at 2 weeks, release averaged 1·21 ± 0·19 ng/mg, which represents 14·7 per cent of release from the sections of aorta. By 6 weeks, release averaged 3·69 ± 0·53 ng/mg, or 44·7 per cent of aorta levels. By comparison, in unseeded grafts at 2 weeks, 6k-$PGF_{1\alpha}$ was undetectable in the incubation mixture. At 6 weeks, there was some release of 6k-$PGF_{1\alpha}$ from the graft sections, averaging 1·28 ± 0·37 ng/mg, or 15·5 per cent of aorta levels.

There was a statistically significant increase in the amount of 6k-$PGF_{1\alpha}$ released from mesothelial cell-seeded grafts when compared with unseeded grafts 6 weeks postoperatively ($P < 0·01$).

Thromboxane release

There was considerable variation in the amounts of TXB_2 released by the sections of graft irrespective of whether they were 2-week or 6-week seeded or unseeded. Levels were also higher than those found in the sections of aorta examined. The most striking difference between release of TXB_2 from sections of aorta and graft was that in the graft sections there was a progressive increase in TXB_2 levels over the 20 min incubation period which was not apparent in the sections of aorta examined (*Table 1*).

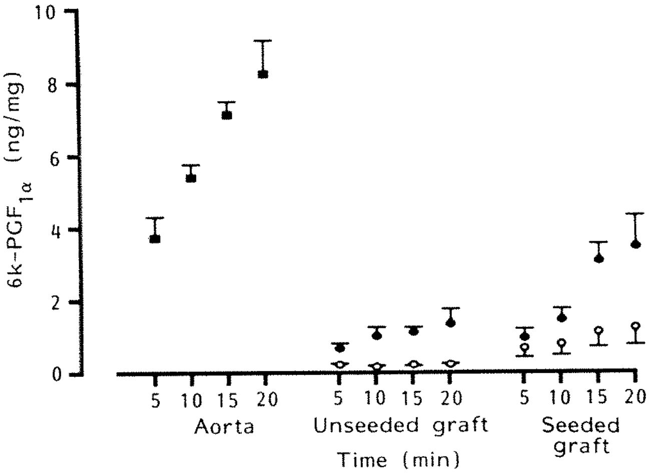


Figure 1 *6k-$PGF_{1\alpha}$ release from sections of aorta (■, n = 8) compared with release from sections of graft either unseeded (n = 4) or seeded (n = 6) with mesothelial cells. The grafts were examined 2 weeks (○) or 6 weeks (●) after implantation. Each point represents the mean release of 6k-$PGF_{1\alpha}$ and the bars indicate ± s.e.m. There was a statistically significant increase in the amount of 6k-$PGF_{1\alpha}$ released from mesothelial cell-seeded grafts 6 weeks after implantation compared with unseeded grafts:* $P < 0·01$

Table 1 *Release of thromboxane from sections of aorta and both unseeded and mesothelial cell-seeded grafts incubated with either 20 μM arachidonic acid or 10 μM A23187*

		Arachidonic acid	A23187
Aorta		0·96	0·85
		1·07	1·02
		1·46	1·43
Graft			
Seeded	2 weeks	2·61	2·20
	6 weeks	2·36	1·19
Unseeded	2 weeks	2·50	1·70
	6 weeks	2·33	1·84

The results are expressed as the cumulative increase in the amount of thromboxane released after 20 min incubation compared with the release after 5 min incubation

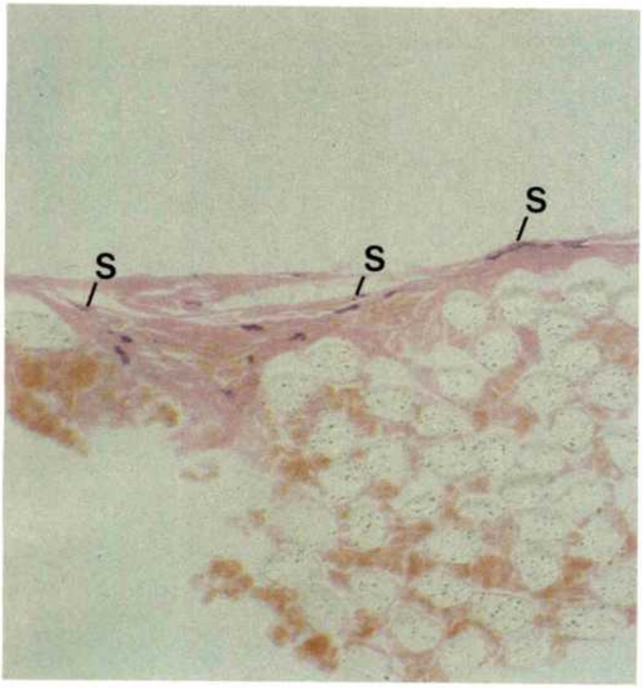


Figure 2 *Light micrograph of a section through a seeded graft before implantation showing the luminal surface covered with a thin layer of fibrin and spindle cells (S) intermixed with red blood cells. Magnification ×400*

Light microscopy

Examination of mesothelial-seeded grafts before insertion revealed the presence of a spindle cell infiltrate (*Figure 2*) not seen in the unseeded grafts.

Discussion

A major shortcoming of small-bore arterial prostheses is their propensity to re-occlude, particularly in the early postoperative days. There are many reasons for this, including surgical technique, the anatomical (run-off) and the physiological (cardiac function) profiles of the recipient, together with the compliance of the implant. However, most research has concentrated upon the lining. The luminal surface of the graft is highly thrombogenic and this may be due to the fact that it is not lined with endothelium.

Natural endothelialization of Dacron arterial grafts, by ingrowth of pannus from the neighbouring vessel, does occur. Data concerning the extent to which this happens show species, as well as location, variation; however, they suggest that, in man, endothelialization is limited to within a few millimetres of the anastomosis[1]. Although some pannus ingrowth of endothelium does occur in dogs, it is slow and incomplete[15] and therefore makes the dog a suitable model; however, as with all animal models, a degree of caution is required in the extrapolation of results to the human situation.

Attempts to improve the postoperative patency of Dacron prostheses have been directed towards 'seeding' the grafts with endothelial cells[4,16]; however, as pointed out by Clarke *et al.*[5], supplies of autologous endothelial cells are not readily available at the time of surgery.

As part of a study designed to assess the feasibility of using autologous peritoneal mesothelial cells as an alternative to endothelial cells for the seeding of vascular prostheses, prostacyclin release by mesothelial-seeded grafts has been compared with that by unseeded grafts and normal aorta. Although only a few animals were used in this series of experiments, the results are encouraging.

PGI_2 release by mesothelial cell-seeded grafts exceeded that of unseeded grafts at 2 and 6 weeks postoperatively. These findings correlate well with the results of our previous study[5], in which the extent of the mesothelial cell coverage was quantified. It was shown that after mesothelial cell seeding there was a partial coverage of the graft lumen with mesothelial cells at 2 weeks and complete coverage by 4 weeks, except for an area adjacent to the anastomosis.

The release of prostacyclin by the unseeded grafts at 6 weeks postimplantation may be attributable to endothelial ingrowth, in the form of capillaries, from the external surface of the graft. Although this phenomenon has not been observed in Dacron prostheses inserted into dogs, it has recently been reported to occur in baboons that received polytetrafluorethylene grafts with increased porosity (60 μm)[17]. Islands of endothelium observed in the centre of Dacron prostheses, also placed in baboons, had previously been speculated to arise from extragraft vascular ingrowth[18].

Prostacyclin functions predominantly in the prevention of platelet aggregation and thrombus formation rather than in the prevention of platelet adhesion to exposed sub-endothelium[19]. It does this by raising platelet cyclic-AMP levels and thus inhibiting endogenous thromboxane synthesis. Studies carried out in rabbits have shown that prostacyclin was unable to inhibit platelet adhesion to aorta after removal of the endothelium but that it was able to restrict the extent of platelet adhesion to a single monolayer and to prevent subsequent platelet aggregation[20]. In this study we have shown that formation of the pseudo-intima 'seeded' with mesothelial cells is associated with increased release of prostacyclin which must be beneficial in reducing the risk of graft re-occlusion.

There is recent evidence that the endothelial cell membrane glycocalyx is also involved in the maintenance of thromboresistance and prevention of platelet adhesion. Removal of cell membrane sialic acid residues by enzyme treatment, potentiates platelet adhesion[21].

Mesothelial cells in an *in vitro* circulation model are able to support blood flow[7], suggesting that they also have an inherently non-thrombogenic surface membrane.

In this study the amount of prostacyclin released by the mesothelial cell-seeded grafts does not reach the levels released by the sections of aorta; however, direct comparisons are difficult because all layers of the aorta have the capacity to release prostacyclin[22] and are probably contributing to the total amount measured in the supernatant, whereas in the mesothelial cell-seeded graft sections, the pseudo-intima is the only definable source of prostacyclin.

Endothelial cells have the capacity to release thromboxane A_2[11,23] and it has been suggested that a decrease in the ratio of PGI_2 to TXB_2 in atherosclerotic tissue and in glutaraldehyde-fixed umbilical vein grafts brings about increased platelet adhesion and thrombogenicity[12,24]. It has not yet been established that mesothelial cells have the capacity to release thromboxane and the results reported here do not clarify this point because, although there was no obvious thrombus formation on the luminal surface of the grafts, platelets adherent to the external surface of the graft sections cannot be excluded as a source of thromboxane. The considerable variation in the release of thromboxane from the graft sections is probably attributable to this fact.

In conclusion, mesothelial cell-seeded Dacron prostheses release more prostacyclin than unseeded grafts at a comparable time after implantation.

These results support the concept originally proposed by Clarke *et al.*[5], that autologous mesothelial cells may well represent a practical alternative to the endothelial cell as a means of reducing platelet consumption and re-occlusion within arterial grafts, particularly in the early postoperative stages.

A detailed longitudinal study is at present under way to characterize further the mesothelial cell-seeded Dacron graft.

Acknowledgements

We are grateful to Dr R. Maini and the support of Vascutek Ltd, Inchinnan, UK, without whose support this work would not have been completed. We would also like to thank the staff of the Wellcome Surgical Unit, Glasgow University Veterinary School, for their assistance during the operations and for their care of the animals.

References

1. Berger KE, Sauvage LR, Rao AM, Wood SJ. Healing of arterial prostheses in man: Its incompleteness. *Ann Surg* 1972; **175**: 118-27.
2. Walton KW, Slaney G, Ashton F. Atherosclerosis in vascular grafts for peripheral vascular disease. Part 2. Synthetic arterial prostheses. *Atherosclerosis* 1986; **61**: 155–67.
3. Herring M, Gardner A, Glover J. A single-stage technique for seeding vascular grafts with autologous endothelium. *Surgery* 1978; **84**: 498–504.
4. Burkel WE, Vinter DW, Ford JW, Kahn RH, Graham LM, Stanley JC. Sequential studies of healing in endothelial seeded vascular prostheses: Histologic and ultrastructure characteristics of graft incorporation. *J Surg Res* 1981; **30**: 305–24.
5. Clarke JMF, Pittilo RM, Nicholson LJ, Woolf N, Marston A. Seeding Dacron arterial prostheses with peritoneal mesothelial cells: a preliminary morphological study. *Br J Surg* 1984; **71**: 492–4.
6. Clarke JMF, Pittilo RM, Machin SJ, Woolf N. A study of the possible role of mesothelium as a surface for flowing blood. *Thromb Haemostas* 1984; **51**: 57–60.
7. Nicholson LJ, Clarke JMF, Pittilo RM, Machin SJ, Woolf N. The mesothelial cell as a non-thrombogenic surface. *Thromb Haemostas* 1984; **52**: 2511–14.
8. Gryglewski R, Bunting S, Moncada S, Flower RJ, Vane JR. Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* 1976; **12**: 685–713.
9. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Prostaglandins* 1976; **12**: 715–37.
10. Herman AG, Claeys M, Moncada S, Vane JR. Biosynthesis of prostacyclin (PGI_2) and 12,1-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) by pericardium, pleura, peritoneum and aorta of rabbit. *Prostaglandins* 1979; **18**: 439–44.
11. Salzman PM, Salmon JA, Moncada S. Prostacyclin and thromboxane A_2 synthesis by rabbit pulmonary artery. *J Pharmacol Exp Ther* 1980; **215**: 240–7.
12. Saldeen P, Esquivel CO, Bjorck C-G, Bergqvist D, Salden T. Thromboxane production in umbilical vein grafts. *Thromb Res* 1984; **33**: 259–68.
13. Bull HA, Pittilo RM, Woolf N, Machin SJ. The effect of nicotine on human endothelial cell release of prostaglandins and ultrastructure. *Br J Exp Pathol* 1988; (in press).
14. Weksler BB, Ley CW, Jaffe EA. Stimulation of endothelial cell prostacyclin production by thrombin, trypsin and the ionophore A23187. *J Clin Invest* 1978; **62**: 923–30.
15. Sauvage LR, Berger KE, Wood SJ, Yates SG II, Smith JC, Mansfield PB. Inter-species healing of porous arterial prostheses. *Arch Surg* 1974; **109**: 698–705.
16. Graham LM, Vinter DW, Ford JW, Kahn RH, Burkel WE, Stanley JC. Endothelial cell seeding of prosthetic vascular grafts. *Arch Surg* 1980; **115**: 929–33.
17. Clowes AW, Kirkman TR, Reidy MA. Mechanisms of arterial graft healing. Rapid transmural capillary ingrowth provides a source of intimal endothelium and smooth muscle in porous PTFE prostheses. *Am J Pathol* 1986; **123**: 220–30.
18. Florey HW, Greer SJ, Poole JCF, Werthessen NT. The development of the pseudointima lining fabric grafts of the aorta. *Br J Exp Pathol* 1962; **43**: 655–60.
19. Higgs EA, Moncada S, Vane JR, Caen JP, Michel H, Toblem G. Effect of prostacyclin (PGI_2) on platelet adhesion to rabbit arterial sub-endothelium. *Prostaglandins* 1978; **16**: 17–22.
20. Eldor A, Falcone DJ, Hajjar DP, Minick CR, Weksler BB. Recovery of prostacyclin production by de-endothelialized rabbit aorta—critical role of the neo-intimal smooth muscle cells. *J Clin Invest* 1981; **67**: 735–41.
21. Gorog P, Schraufstratter I, Born GVR. Effect of removing sialic acids from endothelium on the adherence of circulating platelets in arteries *in vivo*. *Proc R Soc Lond* 1982; **B214**: 471–80.
22. Moncada S, Herman AG, Higgs EA, Vane JR. Differential formation of prostacyclin (PGX or PGI_2) by layers of arterial wall. An explanation for the antithrombotic properties of vascular endothelium. *Thromb Res* 1977; **11**: 323–44.
23. Ingerman-Wojenski C, Silver MJ, Smith JB, Macarak E. Bovine endothelial cells in culture produce thromboxane as well as prostacyclin. *J Clin Invest* 1981; **67**: 1292–6.
24. Saldeen P, Saldeen T. Increased synthesis of thromboxane in atheromatous vessels. *Thromb Res* 1983; **31**: 591–7.

Paper accepted 31 January 1988

Br. J. Surg. 1988, Vol. 75, July,
675–678

Hydroxyethyl starch: an alternative to plasma for postoperative volume expansion after cardiac surgery

C. M. Munsch, E. MacIntyre*, S. J. Machin*, I. J. Mackie* and T. Treasure

*Department of Cardiothoracic Surgery and *Department of Haematology, The Middlesex Hospital, London W1, UK*

Correspondence to:
Mr C. M. Munsch, Cardiac Surgical Research Laboratory, The Baker Medical Research Institute, Commercial Road, Prahran, Victoria 3181, Australia

Hydroxyethyl starch (HES) is a recently developed synthetic volume expander. Forty patients undergoing coronary artery surgery were randomized to receive either HES or plasma protein fraction (PPF) as non-blood volume replacement according to standard haemodynamic criteria. The two groups were comparable in all respects. The median colloid use in the first 24 h was 950 ml (range 500–1500) in the HES group and 975 ml (350–2000) in the PPF group (not significant). There was no difference in blood use, urine output or blood loss between the two groups. Tests of coagulation showed the postoperative changes usual in cardiac surgical patients. There was no difference between the two groups in thrombin time, prothrombin time, activated partial thromboplastin time, or fibrinogen concentration. Similarly, tests of platelet function and Factor VIII and von Willebrand Factor activity showed no difference between the two groups. We conclude that HES is a safe and effective volume expander, and its relative lack of expense and ease of availability make its routine use after cardiac surgery an attractive proposition.

Keywords: Blood coagulation, cardiopulmonary bypass, myocardial revascularization, plasma substitutes, postoperative care

Most patients undergoing open heart surgery require volume expansion in the early postoperative period. Of the available volume expanders plasma protein fraction (PPF) has generally been considered the most suitable, but is expensive and often in short supply. For these reasons, and because of the concern about the safety of human blood products, an alternative colloid volume expander has been sought.

Hydroxyethyl starch (HES), which is a synthetic macromolecule prepared from the waxy species of amylopectin in maize, is available as a 6 per cent solution with a molecular weight average of 450000 (Hespan, 6·0 g/100 ml, Dupont UK). This synthetic colloid has been shown in animal trials[1,2] and clinical studies[3–5] to be an effective volume expander with properties similar to plasma. The routine use of HES after cardiac surgery therefore would appear to be an attractive proposition, but there is concern that HES, like other artificial colloids, may have an adverse effect on the coagulation mechanism[4–6]. This consideration is particularly relevant to patients who have undergone full heparinization and extracorporeal circulation during cardiac surgery.

This study was undertaken to compare the efficacy of HES with PPF after coronary artery surgery and to investigate the effects of HES on the coagulation mechanism.

Patients and methods

Forty consecutive patients undergoing elective coronary artery bypass graft surgery were included in the study. Standard anaesthetic and operative techniques were used and were comparable for all patients. Similarly, standard techniques of cardiopulmonary bypass were employed in all patients, with moderate systemic hypothermia (28°C), and cold potassium cardioplegia for myocardial protection. Intraoperatively only blood recovered for autotransfusion or banked whole blood were used for volume replacement. After surgery the patients were admitted to the intensive care unit where haemodynamic monitoring was instituted and blood was taken for baseline coagulation data (see below).

The patients were then randomly assigned to 2 study groups: 20 patients were allocated to group 1 and received HES as their asanguineous postoperative volume expander; and 20 patients were allocated to group 2 and received PPF. Expansion of the circulating volume was performed according to standard haemodynamic criteria (arterial blood pressure, right atrial pressure, skin/core temperature gradient and urine output). Volume was given as a combination of banked blood and the allocated colloid in such a combination as to maintain the haematocrit between 0·30 and 0·35.

Where indicated, postoperative systemic hypertension was controlled by sodium nitroprusside infusion. Low dose dopamine ($2\text{–}5\,\mu g\,kg^{-1}\,min^{-1}$) and small doses of intravenous frusemide (2·5–5 mg) were administered if indicated by poor urine output ($< 0{\cdot}5\,ml\,kg^{-1}\,h^{-1}$). Arterial blood gas sampling was performed at 4-hourly intervals, and assisted ventilation was continued for as long as clinically indicated. A detailed record was kept of fluid input and output, and blood loss through the chest drains.

Analysis of the patient variables and fluid volume data was performed using non-parametric methods, and are presented as medians and ranges. Wilcoxon's test was used to determine significant differences.

Haematology and coagulation data

On discontinuation of cardiopulmonary bypass, heparinization was reversed with protamine sulphate, controlled by the activated clotting time. Baseline haemostatic tests were performed on return of the patient to the intensive care unit before the administration of any colloid, approximately 60 min after heparin neutralization (sample 1).

Blood was collected into EDTA for full blood and platelet counts (S Plus IV, Coulter Electronics) and into 3·13 per cent trisodium citrate for platelet function and laboratory coagulation tests. Prothrombin time, thrombin time, and activated partial thromboplastin time were measured using standard techniques[7,8]. Fibrinogen was measured by a gravimetric method[9]. Tests of platelet function were performed using a turbidometric method[10] with the Payton Model 300 BD dual channel aggregometer. Final concentrations of aggregating agents were as follows: 0·5–5 μM adenosine diphosphate (ADP) and 1·4 μg/ml collagen.

Factor VIII coagulant activity (fVIII c) was measured by a one-stage assay[9], von Willebrand factor antigen (vWF ag) by rocket immunoelectrophoresis[11], and von Willebrand factor activity (vWF) by a ristocetin cofactor assay using platelet aggregometry[12]. Factor VIII and von Willebrand factor assays were standardized according to the 11th British standard (NIBSC, Hampstead).

All patients received a 300 mg aspirin suppository and intravenous dipyridamole (25 mg/8 h) in the immediate postoperative period. This is a standard therapeutic measure used to enhance coronary graft patency[13,14].

The allocated colloid (HES or PPF) was then administered as indicated by haemodynamic parameters. To compare their effects on the coagulation mechanism all coagulation and haematology tests were repeated after 24 h (sample 2). A blood count was repeated again on the seventh postoperative day.

Analysis of the coagulation data was performed by Student's paired *t* test.

Results

The two groups of patients were comparable regarding age, sex, body weight and surface area, number of grafts performed and period of time spent on cardiopulmonary bypass (*Table 1*). The early postoperative courses of patients in both groups were also comparable (*Table 2*). There were no deaths, and all patients underwent uncomplicated recovery. The length of stay on intensive care unit, the duration of postoperative ventilation and the need for pharmacological intervention were similar in both groups.

The data concerning the fluid balance in the 24 h period after surgery are summarized in *Figure 1*. The median volume of colloid administered to patients in group 1 (HES) was 950 ml (range 500–1500), and to patients in group 2 (PPF) was 975 ml (350–2000). These differences were not significant.

The volumes of banked whole blood administered were similar in both groups; group 1 received a median volume of 830 ml (50–1840) and group 2 a median volume of 830 ml (260–1800). The total, combined, volume of colloid and blood did not differ between the two groups; group 1 received 1700 ml (965–3340), group 2 received 1840 ml (810–3000).

In group 1 median postoperative blood loss through the chest drains was 537 ml (range 240–1265), and in group 2 it was 535 ml (270–1655).

The urine output in the first 24 h after surgery did not differ between the two groups. The median output in group 1 was 1963 ml (range 1043–2600), and in group 2 it was 1728 ml (1088–2866). There was also no difference in urine output in the second 24 h after surgery: group 1, 2346 ml (1526–3785); group 2, 2346 ml (1553–4715).

Coagulation and haematology data

The changes in haemoglobin concentration, haematocrit and platelet count are shown in *Table 3*. The values are all reduced from normal 24 h after surgery: this is to be expected at this stage due to the haemodilutional and the platelet consumptive effects of cardiopulmonary bypass. There were, however, no differences between the two groups, and 7 days postoperatively the values returned to normal in both groups.

The global tests of the coagulation system are shown in *Table 4*. The derangement in clotting factors caused by cardiopulmonary bypass is reflected in the results for sample 1, but there was no difference between the two groups. In sample 2 the prothrombin time in both groups was at the upper limit of normal. This would be expected after cardiopulmonary bypass, and is not clinically important. Over the observation period there was slight shortening of the thrombin time in group 1, but compared with group 2 this difference was not significant. There was a significant increase in the fibrinogen concentration in sample 2 compared with sample 1 in both groups ($P < 0.05$), but no difference between the two groups.

Table 5 shows the results of platelet aggregation studies, which were performed with varying concentrations of ADP and collagen. The results at 24 h are expressed as a percentage of the response seen in the sample taken before the infusion of colloid. This allows direct comparison of the effects of the two colloids and does not attempt to quantify the complex effects of cardiopulmonary bypass on platelet function. For ADP the maximum height of response, and for collagen the angle of the initial slope, were measured and compared. There was a wide range of individual response, but no difference in platelet function was detected between the two groups.

The results of Factor VIII and von Willebrand factor assays are shown in *Table 6*. Again, there was no difference between the two groups in any of these assays.

We did not detect any important differences in the coagulation mechanism as a result of using HES as opposed to PPF. In addition there was no clinical evidence of excessive bleeding in those patients who received HES, neither did we detect any hypersensitivity reactions or other possible side-effects attributable to its use.

Table 1 *Clinical characteristics of study patients*

	Group 1 (HES) $n = 20$	Group 2 (PPF) $n = 20$
Age (years)	59 (43–73)	55 (42–70)
Sex (M:F)	17:3	17:3
Weight (kg)	80·5 (53–105)	77 (46–104)
Surface area (m^2)	1·94 (1·58–2·20)	1·90 (1·41–2·20)
Grafts performed	3 (2–5)	3 (2–5)
Time on bypass (min)	97 (60–152)	98 (52–129)

Results are expressed as the median and range. HES, hydroxyethyl starch; PPF, plasma protein fraction

Table 2 *Early postoperative management*

	Group 1 (HES)	Group 2 (PPF)
Period of ventilation (h) (median and range)	12 (6–21)	12·5 (5–20)
Patients given frusemide	2	3
Patients given SNP	15	15
Patients given dopamine	2	2

SNP, sodium nitroprusside; HES, hydroxyethyl starch; PPF, plasma protein fraction

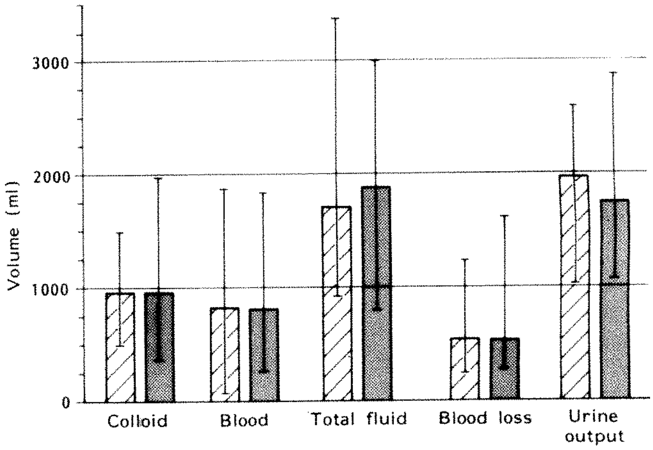


Figure 1 *Fluid balance for the first 24 h postoperatively. The data represent the median and range* ▨, *group 1 (HES)*; ▩, *group 2, (PPF)*

Table 3 *Postoperative changes in haemoglobin, haematocrit and platelet count*

	Twenty-four hours		Seven days	
	Group 1 (HES)	Group 2 (PPF)	Group 1 (HES)	Group 2 (PPF)
Haemoglobin (g dl^{-1})	11·3 ± 0·9	11·1 ± 0·6	12·9 ± 1·3	12·7 ± 1·6
Haematocrit	0·36 ± 0·02	0·37 ± 0·03	0·41 ± 0·04	0·40 ± 0·05
Platelets (× 10^9 l^{-1})	133 ± 29	141 ± 30	321 ± 78	335 ± 42

Results are expressed as the mean ± s.e.m. HES, hydroxyethyl starch; PPF, plasma protein fraction

Table 4 *Postoperative coagulation data*

	Group 1 (HES)		Group 2 (PPF)		
	Sample 1	Sample 2	Sample 1	Sample 2	Normal range
Prothrombin time (s)	15·2 ±1·8	15·0 ±1·6	15·0 ±2·4	14·8 ±1·1	12–15
Thrombin time (s)	15·8 ±3·0	11·5 ±1·6	15·5 ±3·9	12·7 ±2·2	12–14
Activated partial thromboplastin time (s)	47·2 ±8·9	44·6 ±5·6	42·1 ±7·5	39·4 ±3·8	30–40
Fibrinogen (g dl^{-1})	2·32±0·61	3·91±0·88	2·92±0·61	4·29±1·07	1·5–4·0

Sample 1 taken on return to intensive care unit after completion of cardiopulmonary bypass; sample 2 taken 24 h later. Results are expressed as the mean±s.e.m. HES, hydroxyethyl starch; PPF, plasma protein fraction

Table 5 *Postoperative platelet function tests*

Reagent	Group 1 (HES)	Group 2 (PPF)
ADP (0·5 μM)	143·8±50·1	202·8±169·1
ADP (1·0 μM)	137·1±79·9	174·8±116·0
ADP (5·0 μM)	81·0±14·9	72·7± 27·4
Collagen (1 μg ml^{-1})	77·3±43·8	86·1± 44·2
Collagen (4 μg ml^{-1})	90·4±34·2	76·5± 27·3

Results of sample 2 are expressed as a percentage of response seen in sample 1 (mean±s.e.m.). HES, hydroxyethyl starch; PPF, plasma protein fraction

Table 6 *Postoperative Factor VIII assays (sample 2)*

Factor VIII moiety	Group 1 (HES)	Group 2 (PPF)
Factor VIII c (units ml^{-1})	1·18±0·78	1·37±0·46
vWF ag (units ml^{-1})	2·28±0·73	2·62±0·39
vWF (units ml^{-1})	2·11±0·90	2·10±0·84

Results are expressed as the mean±s.e.m. HES, hydroxyethyl starch; PPF, plastma protein fraction

Discussion

Maintenance of the cardiac output, by optimization of filling pressures and adjustment of the circulating volume, is crucial to the management of postoperative cardiac surgical patients. All patients undergoing coronary artery surgery require some degree of plasma volume expansion in the early postoperative period. Apart from the obvious need to replace postoperative blood loss, the pathophysiological effects of hypothermic cardiopulmonary bypass produce a reduction in the effective circulating volume[15] which needs carefully controlled correction in the recovery period.

In common with many other units it has, until now been our practice to use PPF for postoperative volume expansion. However, difficulties with supply and the relative expense of PPF have led us to investigate the suitability of synthetic colloids. The currently available synthetic colloids have important disadvantages, especially in the context of open heart surgery and cardiopulmonary bypass. Dextran 70 has been shown to cause pronounced haemostatic defects and to induce a clinically significant bleeding diathesis[16]. The chemically modified gelatins, on the other hand, are rapidly eliminated and thus do not have a sustained effect as volume expanders. These preparations are also associated with a low, but significant, incidence of anaphylactoid reactions[17].

HES is a new artificial colloid derived from amylopectin, with an average molecular weight of 450000[18]. Substitution with hydroxyethyl groups delays degradation by amylase. Infusion of HES leads to an increase in the circulating volume approximately equal to the volume given, but there is a sustained effect with some 30 per cent augmentation remaining 24 h later. Despite these theoretical advantages clinical experience with HES remains limited in this country, and there remains some uncertainty about its effect on the coagulation mechanism.

Patients undergoing coronary artery surgery provide us with an excellent opportunity for clinical evaluation of HES. Not only is there a need for volume expansion as outlined above, but they provide a homogeneous group undergoing standardized anaesthesia and surgery which is then followed by intensive haemodynamic monitoring. In addition, the haemostatic defects due to cardiopulmonary bypass are likely to be compounded by any haemostatic problems associated with HES. By comparing the volumes of colloid and blood given, this study has shown that HES is at least as effective as PPF in expansion of the circulating volume. There was no clinical evidence of excessive bleeding, and we were unable to detect any other deleterious effects due to the administration of HES.

Before examining the effects of HES on postoperative haemostasis it is necessary to consider the changes induced by the postoperative state in general, by cardiopulmonary bypass in particular, and also by ischaemic heart disease itself. Surgery is known to cause an early fall in the platelet count with a subsequent rise[19], and has the opposite effect on acute phase reactants such as Factor VIIIc and fibrinogen[20]. The prothrombin time and activated partial thromboplastin time are not affected in any consistent manner by surgery, but there may be a shortening of the thrombin time secondary to qualitative and quantitative changes in fibrinogen. Cardiopulmonary bypass has a profound effect on haemostasis[21], brought about by haemodilution and the consumption of platelets and clotting factors (especially factors V and VIII), together with the use of full heparinization and subsequent reversal with protamine. This leads to prolongation of the activated partial thromboplastin time and thrombin time, and a fall in the platelet count. In addition coronary heart disease itself is associated with complex changes in haemostatic factors, particularly an increase in Factor VIIIc and fibrinogen[22].

In this study we have seen the thrombin time shorten over the observation period in both groups. Although this effect appeared to be more marked in the group which received HES, there was no difference between the two groups statistically. It is known that HES macromolecules accelerate the action of thrombin in converting fibrinogen to fibrin. This so-called fibroplastic effect has previously been noted both *in vitro* and *in vivo* and has been reported with dextrans[23,24]. It is not associated with an increased risk of haemorrhage, but impairs elasticity and tensile strength of the fibrin clot, making the clot more lysable by subsequent plasmin digestion. All other observed changes in haemostatic parameters were similar in both groups and represent normal postoperative changes in cardiac surgical patients.

The Factor VIII–von Willebrand factor complex comprises three separate components. The major structural component detected by immunoassay is termed vWF ag. The component concerned with the clotting cascade and measured by a biological assay is fVIII c, while vWF, or von Willebrand factor, refers to the component which facilitates binding of platelets to subendothelial structures and is necessary for platelet agglutination to ristocetin. Major surgery induces a non-specific acute-phase reaction with a rise in all three components. Previously we have shown this rise to be reduced by HES in patients following orthopaedic surgery, and have suggested that this may be due to a protective effect of HES on the vascular endothelium, and may represent a useful antithrombotic strategy[24]. This effect, however, was not seen in the present study, possibly owing to endothelial damage caused by the effects of cardiopulmonary bypass.

Thrombocytopenia is common in patients after cardiopulmonary bypass, owing to haemodilution and sequestration of platelets in the extracorporeal circulation. In addition, synthetic macromolecules may coat the outer membrane of circulating platelets and cause a qualitative platelet function defect. Minor degrees of platelet aggregation abnormalities have previously been observed after infusion of HES[24], but in this study we saw no deleterious effects on platelet numbers or function in the group of patients who received HES.

The prolonged intravascular persistence of HES and the associated maintenance of the colloid oncotic pressure[25,26] is theoretically an important factor in its efficiency as a volume expander and in reducing the risk of tissue and pulmonary oedema. This has prompted the use of HES as an addition to the priming fluid for cardiopulmonary bypass[27,28]. Concern has, however, been expressed about the persistence of HES in the vascular and reticulo-endothelial systems[29], but there is no evidence to date that this is at all detrimental[30].

There is now an accumulating body of evidence that HES is a safe and effective volume expander, not only after cardiac surgery[31-33], but also in resuscitation following severe trauma[34,35]. Some of these studies have used considerably larger volumes of HES than we did (>3000 ml in some cases[33,35]) without reporting any clinically significant deleterious effects on the coagulation system. There have been two recent reports, however, of severe coagulopathy following infusion of 2000 ml of HES (reference 36 and D. N. Lockwood, C. Bullen and S. J. Machin, unpublished results), and we would recommend therefore a volume limit of 1500–2000 ml ($1{\cdot}5$–$2{\cdot}0\,g\,kg^{-1}$) to ensure complete safety.

The current price of HES (£16.72 per 500 ml bottle) compares favourably with that of PPF (£24.15 per 400 ml bottle), and has the further advantage of being readily available[37].

On the basis of this study, therefore, we conclude that HES is a useful alternative to PPF in postoperative cardiac surgical patients, and has advantages in terms of cost and availability.

References

1. Vineyard GC, Bardley BE, Delfaco A. Effect of hydroxyethyl starch on plasma volume and haematocrit following haemorrhagic shock in dogs. Comparison with dextran, plasma and ringer. *Ann Surg* 1966; **164**: 891–9.
2. Ballinger WF, Solanke TF, Thompson WL. The effect of hydroxyethyl starch upon survival of dogs submitted to haemorrhagic shock. *Surg Gynecol Obstet* 1966; **122**: 33–6.
3. Lazrove S, Waxman K, Shippy C, Shoemaker WC. Haemodynamic, blood volume, and oxygen transport responses to albumin and hydroxyethyl starch infusions in critically ill postoperative patients. *Crit Care Med* 1980; **8**: 302–6.
4. Lee WH Jr, Cooper N, Weidner MG Jr, Murner ES. Clinical evaluation of a new plasma expander, hydroxyethyl starch. *J Trauma* 1968; **8**: 381–93.
5. Solanke TF. Clinical trial of 5% hydroxyethyl starch (a new plasma expander). *Br Med J* 1968; **3**: 381–93.
6. Karlson KE, Garzon AA, Shaftan GW, Chu C-J. Increased blood loss associated with administration of certain plasma expanders: dextran 75, dextran 40, and hydroxyethyl starch. *Surgery* 1967; **62**: 670–8.
7. Austen DEG, Rhymes IL. *A Laboratory Manual of Blood Coagulation*. Oxford: Blackwell, 1976.
8. Hardisty RM, Ingram GIC. *Bleeding Disorders—Investigation and Management*. Oxford: Blackwell, 1965.
9. Biggs R. *Human Blood Coagulation, Haemostasis and Thrombosis*. Oxford: Blackwell, 1976.
10. Born GVR. Quantitative investigations into the aggregation of blood platelets. *J Physiol* 1962; **162**: 67–71.
11. Laurell CB. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Anal Biochem* 1966; **15**: 45–69.
12. Weiss HJ, Hoyer LW, Rickles FR, Varma A, Rogers J. Quantitative assay for a plasma factor deficient in von Willebrand's disease that is necessary for platelet aggregation. *J Clin Invest* 1983; **52**: 2708–10.
13. Cheseboro JH, Clements IP, Fuster V. A platelet inhibitor drug trial in coronary artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein graft patency. *N Engl J Med* 1982; **307**: 73–8.
14. Mayer JE Jr, Lindsay WG, Castaneda W, Nicoloff DM. Influence of aspirin and dipyridamole on patency of coronary artery bypass grafts. *Ann Thorac Surg* 1981; **31**: 204–10.
15. Cleland J, Pluth JR, Tauxe WN, Kirklin JW. Blood volume and body fluid compartment changes soon after closed and open intracardiac surgery. *J Thorac Cardiovasc Surg* 1966; **52**: 698–705.
16. Mishler JM. Synthetic plasma volume expanders—their pharmacology, safety and clinical efficacy. *Clin Haematol* 1984; **13**: 75–92.
17. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **i**: 466–8.
18. Mishler JM. *Pharmacology of Hydroxyethyl Starch. Use in Therapy and Blood Banking*. Oxford, New York: Oxford University Press, 1982.
19. Brozovic M. Physiological mechanisms in coagulation and fibrinolysis. *Br Med Bull* 1977; **33**: 231–8.
20. Lombardi R, Mannucci PM, Seghatchian MJ, Garcia V, Coppola R. Alterations of factor VIII von Willebrand factor in clinical conditions associated with an increase in its plasma concentration. *Br J Haematol* 1981; **49**: 61–8.
21. Kalter RD, Saul CM, Wetstein L, Soriano C, Reiss RF. Cardiopulmonary bypass. Associated haemostatic abnormalities. *J Thorac Cardiovasc Surg* 1979; **77**: 428–35.
22. Editorial. Haemostatic factors and coronary heart disease. *Lancet* 1981; **i**: 22–3.
23. Muzaffar TZ, Stalker AL, Bryce WAJ, Dhall DP. Dextrans and fibrin morphology. *Nature* 1972; **238**: 288–90.
24. MacIntyre E, Mackie IJ, Ho D, Tinker J, Bullen C, Machin SJ. The haemostatic effects of hydroxyethyl starch used as a volume expander. *Intensive Care Med* 1985; **11**: 300–3.
25. Haupt MT, Rackow EC. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin and saline solutions. *Crit Care Med* 1982; **10**: 159–62.
26. Barclay SA, Bennet ED. Hydroxyethyl starch increases colloid osmotic pressure and central venous pressure in critically ill patients. *Clin Sci* 1985; **68**: (Suppl II), 27 (abstract).
27. Palanzo DA, Parr GVS, Bull AP, Williams DR, O'Neill MJ, Waldhausen JA. Hetastarch as a prime for cardiopulmonary bypass. *Ann Thorac Surg* 1982; **34**: 680–3.
28. Sade RM, Crawford FA, Dearing JP, Stroud M. Hydroxethyl starch in priming fluid for cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1982; **84**: 35–8.
29. Boon JC, Jesch F, Ring J, Messmer K. Intravascular persistence of hydroxyethyl starch in man. *Eur Surg Res* 1976; **8**: 497–503.
30. Yacobi A, Stoll RG, Sum CY, Lai CM, Gupta SD, Hulse JD. Pharmacokinetics of hydroxyethyl starch in normal subjects. *J Clin Pharmacol* 1982; **22**: 206–12.
31. Diehl JT, Lester JL, Cosgrove DM. Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg* 1982; **34**: 674–9.
32. Moggio RA, Cook Chan Rha, Somberg ED, Praeger PI, Pooley RW, Reed GE. Haemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med* 1983; **11**: 943–5.
33. Kirklin JK, Lell WA, Kouchoukos NT. Hydroxyethyl starch *versus* albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg* 1984; **37**: 40–6.
34. Puri VK, Paidipaty B, White L. Hydroxyethyl starch for resuscitation of patients with hypovolaemia and shock. *Crit Care Med* 1981; **9**: 833–7.
35. Shatney CH, Deepika K, Militello PR, Majerus TC, Dawson RB. Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg* 1983; **118**: 804–9.
36. Cully DC, Larson CP, Silverberg GD. Hetastarch coagulopathy in a neurosurgical patient. *Anesthesiology* 1987; **66**: 707–8.
37. Monthly Index of Medical Specialities (MIMS). September 1987.

Paper accepted 23 January 1988

Br. J. Surg. 1988, Vol. 75, July, 679–681

Clinical observations on the wound healing properties of honey

S. E. E. Efem

University Department of Surgery,
University Teaching Hospital,
Calabar, Nigeria

Correspondence to:
Mr S. E. E. Efem

Fifty-nine patients with wounds and ulcers most of which (80 per cent) had failed to heal with conventional treatment were treated with unprocessed honey. Fifty-eight cases showed remarkable improvement following topical application of honey. One case, later diagnosed as Buruli ulcer, failed to respond. Wounds that were sterile at the outset, remained sterile until healed, while infected wounds and ulcer became sterile within 1 week of topical application of honey. Honey debrided wounds rapidly, replacing sloughs with granulation tissue. It also promoted rapid epithelialization, and absorption of oedema from around the ulcer margins.

Keywords: Wound healing, honey

Despite recent advances in antimicrobial chemotherapy and wound management, several types of wounds and ulcers still prove recalcitrant to treatment. There is no scarcity of such recalcitrant ulcers in the Tropics. Experimental evidence suggests that honey accelerates wound healing in mice[1] and the present study investigates the healing properties of honey in man.

Patients and methods

Clinical observations on the wound healing properties of honey were made in 59 consecutive referred patients at the University of Calabar Teaching Hospital between January 1984 and December 1986. All of the patients had single ulcers; 47 (80 per cent) of them were referred because the ulcers had failed to heal with conventional treatment methods, such as Eusol toilet, dressings (with acriflavine, Sofra-Tulle (Raussel, Middlesex, UK) or Cicatrin (Calmic, Crewe, UK)) or topical and systemic antibiotics. All had been treated for what the clinicians deemed a 'sufficiently long time' (1 month to 2 years) but showed no signs of healing or were increasing in size.

Swabs were taken from the ulcers for culture and sensitivity determinations before starting treatment. After cleaning the wound with normal saline, 15–30 ml of fresh unprocessed honey obtained from bee hives was applied as a daily dressing. After 1 week another wound swab was taken for culture and sensitivity.

Five patients had their ulcer biopsied because of the suspicion of malignancy while ten patients had X-rays to exclude bone involvement.

The wounds were inspected daily at the time of dressing and the appearance of the ulcer and surrounding tissues was recorded. In one patient with a Buruli ulcer, dressing with honey was discontinued after 2 weeks because the wound was increasing rapidly in size. This patient was placed on systemic therapy with rifampicin 150 mg and isonicotinic acid hydrazide 100 mg thrice daily and streptomycin 1 g intramuscularly daily.

Pure cultures of *Pseudonomas pyocyanea*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus mirabilis* and *Escherichia coli* were tested *in vitro* for sensitivity to honey.

Forty-one patients were treated as in-patients while 18 patients were treated as out-patients; 13 patients had skin grafting.

Results

There were 47 males and 12 females and their ages ranged from 2 months to 78 years. The diagnoses of the various ulcers are given in *Table 1*. There were 55 benign ulcers and 4 malignant ulcers. The benign ulcers included 4 diabetic ulcers and one Buruli ulcer. All the benign ulcers responded well to treatment except the Buruli ulcer which increased in size until therapy with honey was stopped. The various organisms isolated from swab culture are listed in *Table 2*. *Mycobacterium ulcerans* was isolated from the patient who was subsequently diagnosed as having a Buruli ulcer.

The histology reported revealed squamous cell cancer in four patients. Three of these patients had limb amputation while one had wound excision before skin grafting.

Swabs from 51 wounds which yielded growth of organisms initially, yielded no growth when the second wound swab cultures were performed 1 week after dressing with honey.

Sloughs and necrotic and gangrenous tissues gradually separated from the floor and wall of the ulcers so that they could be lifted with a pair of forceps without patients feeling any pain. Surrounding oedema subsided, weeping ulcers were dehydrated and foul-smelling wounds were rendered odourless within 1 week of dressing with honey.

Sloughs and necrotic tissues were rapidly replaced with granulation tissue and advancing epithelialization. Early burn wounds healed quickly and were not colonized by bacteria.

Four patients whose diabetes had proved difficult to control became controlled after successful sterilization of their ulcers

Table 1 *Types of wounds and ulcers treated with honey*

Wounds	No. of cases
Fournier's gangrene	13
Burn wounds	10
Tropical ulcer	6
Traumatic ulcer	6
Cancrum oris	5
Bed sore	4
Diabetic ulcer	4
Sickle cell malleolar ulcer	4
Malignant ulcers	4
Extra-oral cancrum	2
Buruli ulcer	1
Total	59

Table 2 *Swab culture result from 51 ulcers with positive results*

Type of organism	Frequency of organisms	(%)
Pseudomonas pyocyanea	35	32
Escherichia coli	31	28
Staphylococcus aureus	15	14
Proteus mirabilis	9	8
Mixed coliforms	9	8
Klebsiella species	7	6
Streptococcus faecalis	3	3
Streptococcus pyogenes	1	1
Total	110	100

0007–1323/88/070679–03$3.00 © 1988 Butterworth & Co (Publishers) Ltd

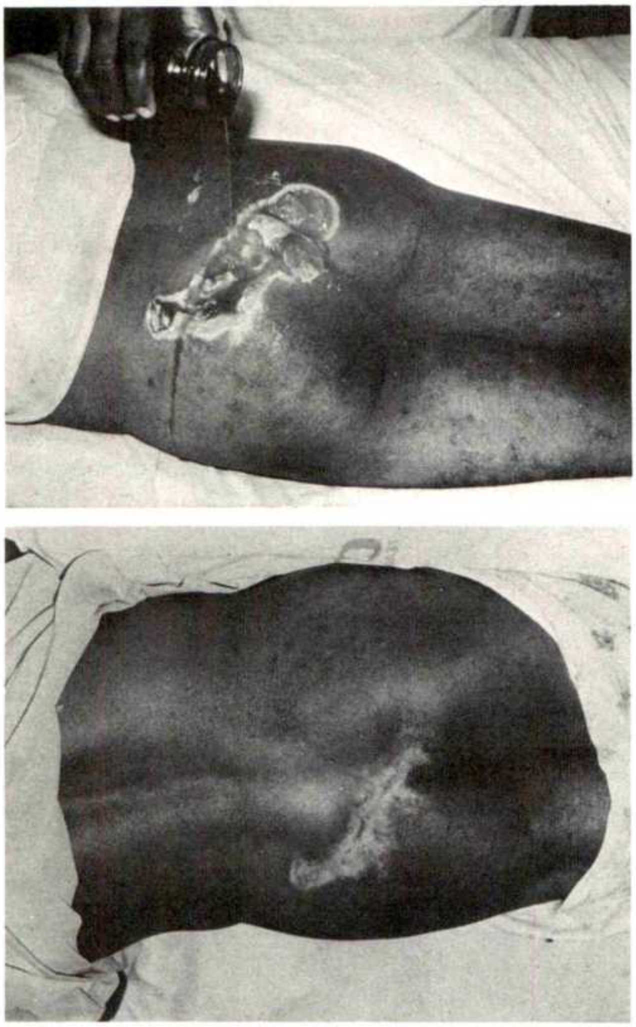


Figure 1 (**a**) *A bedsore before treatment. Note the island of slough separating from the edges of the deep bedsore.* (**b**) *The healed bedsore after topical application of honey without any need for skin grafting*

with honey. Amputation was avoided after successful treatment of their ulcers with honey and skin grafting.

In vitro sensitivity tests, as demonstrated by a drop of honey on culture plates containing pure cultures, did not show complete lysis of *P. pyocyanea*, as was the case with other organisms, even though wounds from which *P. pyocyanea* was isolated were completely sterilized *in vivo*. Therefore honey may be more active *in vivo* than *in vitro*.

No allergy or other adverse reaction was observed during this study. Some of the wounds treated with honey are shown in *Figures 1* and *2*.

Discussion

Although it has been known for more than 100 years[1] that honey can accelerate wound healing, there have been only isolated reports of its use in the healing of burns, decubitus ulcers, infected wounds and open wounds from radical vulvectomy[2-7]. The present study is the first large-scale clinical study carried out to assess the use of honey for wound healing.

The physical, chemical and biological properties of honey have been documented[8-14]. The properties as observed in this study included: debridement of wounds by a chemical or enzymatic action; absorption of oedema fluids around wounds; inactivation of bacteria; deodorization of offensive wounds; promotion of granulation tissue formation and epithelialization; and improvement of nutrition. However, such properties as debridement of wound, deodorization of offensive wounds, absorption of oedema fluids around wounds and improvement of nutrition had not been described before. The bacteriocidal activity of honey was well demonstrated by this study and it appears to be more powerful *in vivo* than *in vitro*. All the organisms isolated from wounds in this study were susceptible to honey with the exception of *M. ulcerans*. The resistance of *M. ulcerans* to honey may be due to the high lipid content of its cell wall preventing dehydration of the bacteria and also preventing penetration by inhibine, the thermolabile[11] bacteriocidal substance[10-12] present in honey. The antibacterial activity may also be due to the low pH of 3·6 and hygroscopic properties of honey. The viscose barrier formed by honey also prevents sterile wounds from being penetrated and colonized by bacteria[1].

The chemical debridement action of honey was of greatest advantage in Fournier's gangrene, cancrum oris and decubitus ulcers as the sloughs in these ulcers separated in 2–4 days but took much longer in other types. Chemical debridement with honey apart from accelerating wound healing spared these patients the necessity for surgical debridement under general anaesthesia.

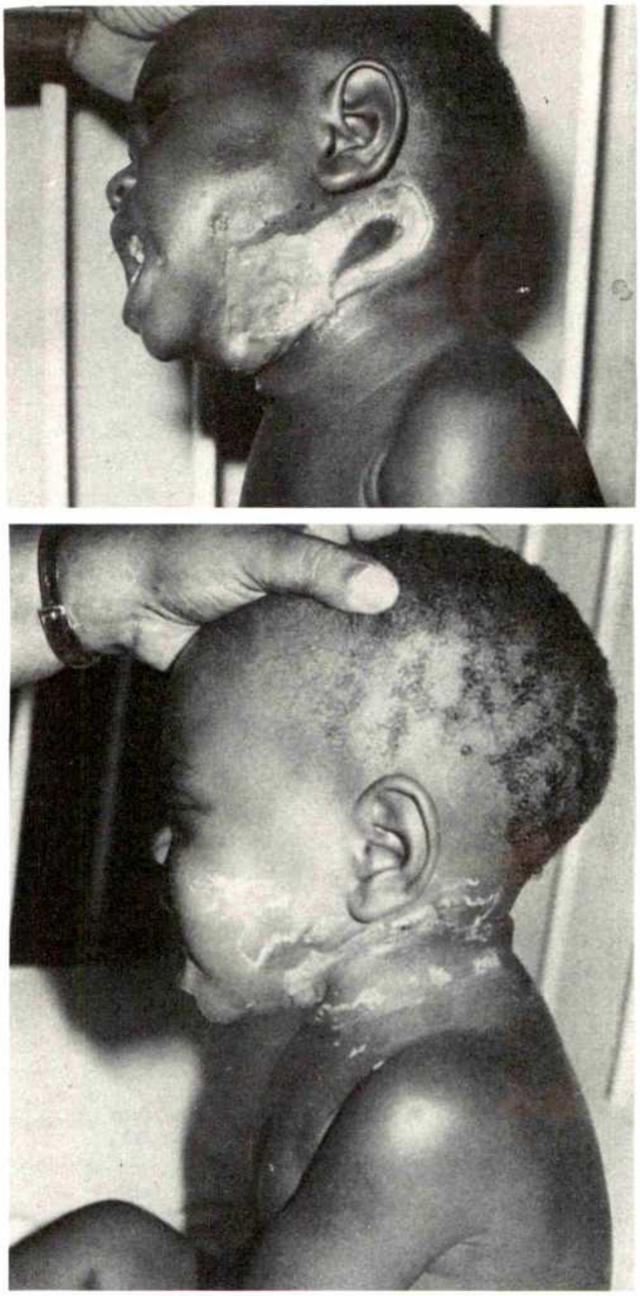


Figure 2 (**a**) *Appearance of an extra-oral cancrum on admission.* (**b**) *The same patient after topical application of honey for 3 weeks*

The hygroscopic property of honey enables it to dehydrate bacteria rendering them inactive and to dehydrate oedematous and soggy wounds reducing their surface area and making them more clearly defined. This property was of greatest advantage in diabetic and malignant ulcers enabling a definite decision to be made on whether to amputate the affected limb. Dehydration of unwanted tissue fluids around the ulcer might also decrease tissue turgor and improve tissue oxygenation and hence wound healing.

In conclusion honey, appears to have several important properties that make it ideal as a dressing agent for almost every type of wound or ulcer except those infected with mycobacteria.

Acknowledgements

I wish to thank my colleagues especially Professor J J. Andy for referring some of the interesting cases to me. I wish also to thank Dr K. T. Udoh for assisting in the bacteriological studies.

References

1. Bergam A, Yanai J, Weiss J, Bell D, David MP. Acceleration of wound healing by topical application of honey: An animal model. *Am J Surg* 1983; **145**: 374–6.
2. Phillips CE. Honey for burns *Gleanings in Bee Culture* 1933; **61**. 284.
3. Voigtlander H Honey for burns and scalds *The Bee World* 1937; **18**: 128.
4. Bulman MW. Honey as a surgical dressing. *Middlesex Hosp J* 1955; **55**: 188–9.
5. Temnov VA Bactericidal properties of honey and other beekeeping products for the healing of wounds. *Bee World* 1944; **25**: 86–7.
6. Blomfield R Honey for decubitus ulcers. *J Am Med Assoc* 1973, **224**. 905.
7. Cavanagh D, Beazler J, Ostapowicz F. Radical operation for carcinoma of the vulva, a new approach for wound healing. *J Obstet Gynaecol Br Commonw* 1968; **77**. 1037–40.
8. White JA Composition of honey. In Crane E, ed Honey—a Comprehensive Survey. London: Heinemann, 1975: 157–206.
9. Hunt TK. Recent advances in wound healing. *Ann Surg* 1970, **2**: 1–10.
10. White JW, Subers MH, Schepartz AI. The identification of inhibine. *Am Bee J* 1962; **102**: 430–1.
11. Khristov G, Mladenov S. Honey in surgical practice: the antibacterial properties of honey. *Khirurgiya* 1961, **14** 937–45.
12. White JW, Subers MH, Schepartz AI. The identification of inhibine. The antibacterial factor in honey as hydrogen peroxidase and its origin in a honey glucose oxidase system. *Biochem Biophys Act* 1963, **73**: 57–70.
13. Gonnet M, Lavie P. Influence du Chauflage Sur la facteur antibiotique present dans les miels *Ann Abeille* 1960, **3**: 349–69.
14. Lindner KE. Ein Beitrag zur frage der antimikrobiellen wirkung der naturhonige. *Zentrablatt der Bakteriologie und Parasitologie* 1962, **115**: 720–36.

Paper accepted 24 January 1988

Change of address

Please note that from 13 June 1988 the editorial office is moving to Butterworth Scientific Ltd. Please send all correspondence to:

Lynne Ponjee,
Editorial Secretary,
Butterworth Scientific Ltd.,
PO Box 63, Westbury House,
Bury Street, Guildford,
Surrey GU2 5BH, UK
Telephone: 0483 301439

Br. J. Surg. 1988, Vol. 75, July,
682–685

Effect of surgery on neutrophil functions, superoxide and leukotriene production

Perioperative changes of neutrophil function were investigated in 28 patients who underwent major surgery, particularly focusing on the potential capacity for superoxide and leukotriene production, which seem to be important in host defence. The superoxide-producing capacity of neutrophils, which was examined using N*-formyl-peptide or phorbol myristate acetate as an attractant, significantly decreased postoperatively to 55 and 69 per cent of the pre-operative values, respectively. The leukotriene-producing capacity of neutrophils, which was stimulated with calcium ionophore A23187 in the presence of arachidonic acid, significantly changed postoperatively. The leukotriene B_4 (LTB_4) production increased together with an increment of production of* 6-trans *6-trans LTB_4, however, increased postoperatively to 1·2 times the (LTC_4) production decreased postoperatively. The total production of leukotriene A_4 (LTA_4) metabolites consisting of LTB_4, LTC_4, and 6-trans LTB_4, however, increased postoperatively to 1·2 times the pre-operative values. This indicates that neutrophils in the postoperative period have a higher capacity for LTA_4 production but a lower capacity for superoxide production than those in the pre-operative period.*

Keywords: Neutrophil, surgery, superoxide, leukotriene

J. Utoh*†,
T. Yamamoto†,
T. Utsunomiya†,
T. Kambara†, H. Goto*
and Y. Miyauchi*

**The First Department of Surgery,*
and †Department of Allergy,
Institute for Medical Immunology,
Kumamoto University Medical
School, Kumamoto, Japan
Correspondence to: Dr J. Utoh,
The First Department of Surgery,
Kumamoto University Medical
School, 1-1-1 Honjo,
Kumamoto 860, Japan

It is well known that patients who have received major surgery have a high risk of bacterial infection. There is no doubt that one of the most important cells in host defence against bacterial infection is the neutrophil, which ingests and kills bacteria by producing oxygen radicals as well as other chemical mediators. Usually, systemic neutrocytosis is observed after major surgery; however, despite the increase in neutrophil numbers, bacterial infection still occurs. One of the possible causes of this may be an impairment of neutrophil function at this period.

Previous investigators have reported effects of surgery on such neutrophil functions as chemotaxis[1–3], phagocytosis[4], lysosomal enzyme content[5], and respiratory burst[2,6]. However, the basic stimulus of surgery in altering these neutrophil functions is still not established, as some reports showed the deterioration of neutrophil function[2,4–6] but others did not[1,3].

Recent advances in biomedical technology have made it possible to analyse molecules produced by neutrophils, qualitatively as well as quantitatively. Among the molecules which neutrophils generate, oxygen radicals such as superoxide, hydrogen peroxide and hydroxyl radicals are considered to be important in bacterial killing. An impairment in the generation of these molecules brings a high risk of bacterial infection, as shown in chronic granulomatous disease patients[7,8].

Neutrophil-derived leukotrienes also seem to have important roles in host defence. For instance, leukotriene B_4 (LTB_4) is a potent chemo-attractant for neutrophils[9,10]; it also enhances the natural killing activity of lymphocytes[11] and induces gamma-interferon production by them[12]. LTC_4 as well as LTD_4 induces smooth-muscle contraction and increases microvascular permeability[13,14]. An impairment of leukotriene generation is thought to increase the risk of bacterial infections.

In the present study, therefore, we investigated the perioperative alteration of neutrophil functions, focusing on the capacities for superoxide and leukotriene production, a subject which has not been reported on previously.

Patients and methods

Patients and surgical procedure

A total of 28 patients (13 men and 15 women) who underwent major surgery are included in this study. Of these, 11 patients underwent open heart surgery and 17 patients underwent abdominal surgery, including 10 patients with malignancy. Their ages ranged from 19 to 67 years (mean 52·4 years). All patients were uniformly anaesthetized with endotracheal intubation and maintained with inhalation agents, narcotics, and pancuronium.

Reagents

Hanks' balanced salt solution (HBSS) was purchased from Nissui, Tokyo, Japan. Cytochrome *c*, *N*-formyl-methionyl-leucyl-phenylalanine (FMLP), phorbol myristate acetate (PMA), superoxide dismutase (SOD), calcium ionophore A23187, and arachidonic acid were obtained from Sigma Chemical Co., St. Louis, Maryland, USA. Novapak C-18 column (ultrasphere octadesil silica; 3·9 × 150 mm) was purchased from Waters Associate, Milford, Massachusetts, USA. Purified leukotrienes were kindly donated by Ono Pharmaceutical Co., Osaka, Japan.

Neutrophil preparation

Peripheral venous blood, anticoagulated with heparin sodium (10 units/ml), was obtained from each patient on the pre-operative and the first postoperative days. The leucocyte count was measured using a Coulter Counter Model-S (Coulter Electronics, Hialeah, France), and leucocyte differential values for individual cell types were determined with Giemsa-stain smears. The neutrophil preparation from heparinized blood was performed according to the method of Böyum[15]. Briefly, purified neutrophils were isolated by means of dextran sedimentation followed by centrifugation on a Hypaque–Ficoll gradient and hypotonic lysis of red blood cells. The cells were suspended in HBSS (pH 7·2) and adjusted to a concentration of 6×10^6 cells/ml. The proportion of neutrophils in the cell preparation was more than 95 per cent.

Assay of superoxide production

The assay of the superoxide-producing capacity of neutrophils was performed according to the method described by Newburger *et al.*[16]. Briefly, neutrophils (3×10^5 cells) in 1 ml of HBSS which contained cytochrome *c* (5×10^{-5} M) were pre-incubated for 5 min at 37°C. FMLP (5×10^{-7} M) or PMA (50 ng/ml) was used as a stimulant and the reaction was continuously observed by monitoring the absorbance at 550 nm at 37°C using a spectrophotometer (Hitachi, Tokyo, Japan). To determine whether the cytochrome *c* reduction was attributable to superoxide, SOD was introduced into the assay mixture at a final concentration of 50 μg/ml.

Table 1 *Perioperative changes in leucocyte numbers in peripheral blood*

	Before operation	After operation
Total leucocyte number, × 10^9/l	5·80 ± 1·33 (100)	*10·03 ± 3·77 (100)
Subpopulation, × 10^9/l		
Basophil	0·03 ± 0·02 (1)	0·07 ± 0·02 (1)
Eosinophil	0·25 ± 0.16 (4)	0·29 ± 0·13 (3)
Stab	0·23 ± 0·13 (4)	*1·80 ± 0·76 (18)
Segment	3·22 ± 1·32 (56)	*5·82 ± 2·19 (58)
Lymphocyte	1·81 ± 0·71 (31)	1·74 ± 0·82 (17)
Monocyte	0·26 ± 0·18 (4)	0·31 ± 0·27 (3)

Data are shown as mean ± s.d.; percentages in parentheses
* Values considered to be significant by paired *t* test (*P* < 0·05 *versus* pre-operative values)

Assay of leukotriene production

The assay of the leukotriene-producing capacity of neutrophils was performed according to previously described methods[17–20], with some modifications. Neutrophils (6 × 10^6 cells) in 1 ml of HBSS were pre-incubated for 10 min at 37°C. Calcium ionophore A23187 (2 × 10^{-6} M) and arachidonic acid (5 × 10^{-5} M) were then added as stimulants and incubated for 5 min at 37°C. After this, the reaction was terminated by the addition of fivefold volume of methanol and the leukotrienes were extracted for 1 h at 4°C in the same solution. The samples were centrifuged to remove the leucocytes at 1500*g* for 20 min and the supernatants were evaporated by a centrifugal evaporator (Savant, New York, USA). The dried materials which contained leukotrienes were dissolved in 60 μl of 50 per cent methanol. Identification and quantification of each leukotriene in these samples were performed by a reversed phase high performance liquid chromatography (HPLC) using a Novapak C-18 column connected to a HPLC system (Toyosoda, Tokyo, Japan), with a flow rate of 0·5 ml/min, monitoring the absorbance at 280 nm As a mobile phase buffer, acetonitrile–methanol–water–acetic acid (33:9·57·1, pH adjusted to 5·6 with ammonium hydroxide) was used. Ten microlitres of each sample were applied for the analysis. As standard materials, 10 ng of purified leukotriene were also applied to the same column

Statistical analysis

A paired Student's *t* test was used for comparison of pre- and postoperative values. Data are expressed as mean ± standard deviation (s.d.).

Results

Perioperative changes of peripheral neutrophil counts

Leucocyte numbers and sub-populations in peripheral blood at pre- and postoperative periods are shown in *Table 1*. Peripheral leucocyte numbers significantly increased postoperatively. These changes were mainly due to the increase in neutrophils: an increment of stab form neutrophils was particularly observed. The populations of basophils and eosinophils were not changed significantly.

Superoxide production

Perioperative changes in superoxide-producing capacity of the neutrophils are shown in *Table 2*. FMLP was used as a stimulant for all neutrophil analysis and PMA was used in eight cases. On the first postoperative day, the superoxide production examined by FMLP significantly decreased to 55 per cent of the pre-operative values. The superoxide production stimulated by PMA also significantly reduced to 69 per cent of the pre-operative values.

Leukotriene production

Figure 1 shows patterns typical of the HPLC analysis. In this case, neutrophils were obtained on pre- and postoperative days from a 52-year-old male patient who underwent colectomy. The LTB$_4$-producing capacity increased postoperatively, together with an increment in the production of 6-*trans* LTB$_4$ and ω-oxidates of LTB$_4$. In contrast to this, the LTC$_4$-producing capacity decreased postoperatively. LTD$_4$ was detected neither in pre- nor postoperative samples.

The perioperative changes of leukotriene-producing capacity of the neutrophils obtained from 28 patients are shown in *Table 2*. Before operation, the LTB$_4$- and LTC$_4$-producing capacities were 17·9 ± 4·2 ng LTB$_4$/10^6 cells and 11·8 ± 4·4 ng

Table 2 *Perioperative changes in superoxide- and leukotriene-producing capacities of neutrophils*

	Before operation	After operation
Superoxide production (nmol O_2^-/10^6 cells per min)		
stimulated by FMLP (*n* = 28)	17·4 ± 4·5	* 9·6 ± 2·7
PMA (*n* = 8)	31·2 ± 6·1	*21·5 ± 5·8
Leukotriene production (%) stimulated by A23187 (*n* = 28)		
LTB$_4$	100	*147 ± 54
6-*trans* LTB$_4$	100	*175 ± 67
ω-oxidates of LTB$_4$	100	*123 ± 22
LTC$_4$	100	* 37 ± 28
LTD$_4$	n.d.	n.d.

Data are expressed as mean ± s.d.
* Values considered to be significant by paired *t* test (*P* < 0·05 *versus* pre-operative values)
FMLP, *N*-formyl-methionyl-leucyl-phenylalanine (5 × 10^{-7} M); PMA, phorbol myristate acetate (50 ng/ml); A23187, calcium ionophore A23187 (2 × 10^{-6} M); n.d., not detected

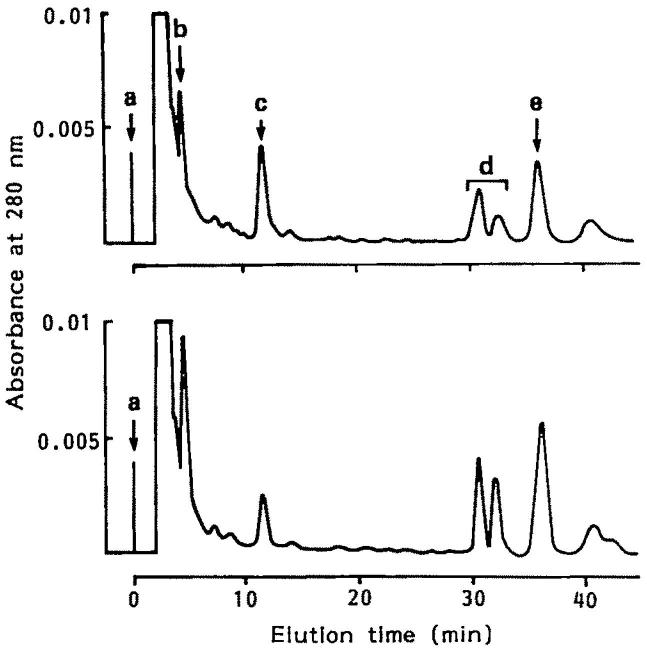


Figure 1 *Reversed phase high performance liquid chromatographic (HPLC) profiles of leukotrienes which were generated from neutrophils of a 52-year-old male patient who underwent colectomy. Neutrophils were obtained on pre-operative (upper) and postoperative (lower) days and incubated with calcium ionophore A23187 (2 × 10^{-6} M), and arachidonic acid (5 × 10^{-5} M) followed by the extraction of leukotrienes with methanol. After centrifugation of the extract, the supernatant was concentrated and applied to HPLC with a Novapak C-18 column, using a mobile phase buffer containing acetonitrile–methanol–water–acetic acid (33.9·57.1, pH 5·6) The flow rate was 0·5 ml/min and absorbance at 280 nm was recorded Each product was compared with purified leukotrienes for its elution time.* **a**, *injection;* **b**, *ω-oxidates of LTB$_4$;* **c**, *LTC$_4$,* **d**, *6-*trans *LTB$_4$;* **e**, *LTB$_4$*

LTC$_4$/10^6 cells, respectively. These values were considered to be within the normal range, based on those of neutrophils from healthy volunteers, which gave values of $17{\cdot}7 \pm 5{\cdot}5$ ng LTB$_4$/10^6 cells and $12{\cdot}8 \pm 4{\cdot}9$ ng LTC$_4$/10^6 cells, respectively. After operation, LTB$_4$ production increased significantly, together with an increment in the production of 6-*trans* LTB$_4$ and ω-oxidates of LTB$_4$; LTC$_4$ production, however, decreased significantly after operations. LTD$_4$ was not detected in any cases in the pre- or postoperative periods.

Discussion

There are several reports showing postoperative impairment of such neutrophil functions as chemotaxis[2], lysosomal enzyme content[5], and respiratory burst[4,6]. In the present study we investigated the perioperative alteration of neutrophil function at the molecular level, focusing on the potential capacity for superoxide and leukotriene production. Superoxide production was significantly diminished in the postoperative period, an observation which is consistent with previous reports for the reduced respiratory burst[2,4]. The alteration in leukotriene production, however, has not been reported previously.

In the present study, we initially used FMLP as a stimulant for superoxide generation of the neutrophils. As the structure of the strong chemotactic peptide, FMLP, is indeed contained in bacterial protein products, it seemed to be a most suitable stimulant for analysis of the neutrophil function against bacterial infection. However, it became important to investigate whether the impairment of response to FMLP was a reflection of the decrease in total capacity of superoxide production or attributable to a reduction in this particular receptor-mediated reaction. Therefore, we also conducted tests using PMA, which is known to be a direct stimulator of intracellular protein kinase C[21], to investigate the maximum potential capacity of the neutrophils. The response to PMA decreased during postoperative period to an extent similar to that of FMLP (*Table 2*). These results suggest that the reduced response to FMLP is probably a reflection of the lower level of the superoxide-producing capacity of the neutrophils in the postoperative period.

In the leukotriene-producing study we used calcium ionophore A23187 which, like PMA, directly stimulates intracellular protein kinase C[21]: leukotriene production as a response to FMLP was not detectable. The results of leukotriene production in the present study, therefore, reflect the changes in the total potential capacity of the neutrophils. The LTB$_4$-producing capacity increased significantly, concomitantly with an increment in the production of 6-*trans* LTB$_4$ and ω-oxidates of LTB$_4$. On the other hand, the LTC$_4$-producing capacity decreased significantly. LTB$_4$, 6-*trans* LTB$_4$, and LTC$_4$ are known to be metabolites of LTA$_4$[22] (*Figure 2*). Both LTB$_4$ and LTC$_4$ were reported to be generated enzymatically from LTA$_4$; 6-*trans* LTB$_4$ was claimed to be a non-enzymatic metabolite of LTA$_4$[22–24]. This phenomenon could be interpreted as a shift of LTA$_4$ metabolism from the LTC$_4$-producing pathway to the LTB$_4$-producing one. However, there may not be a single cause, because when the total amount of these three LTA$_4$ metabolites was compared in the pre- and postoperative periods, the postoperative value was 1·2 times higher than the pre-operative one (*Table 2*). Therefore, it can be inferred that neutrophils during the postoperative period have a higher LTA$_4$ production than those in the pre-operative period. The high LTA$_4$ production in neutrophils during the postoperative period may affect the increase in production of LTB$_4$ and 6-*trans* LTB$_4$. The low postoperative neutrophil LTC$_4$ production may be attributable to a decrease in neutrophil LTC$_4$ synthetase (glutathione *S*-transferase).

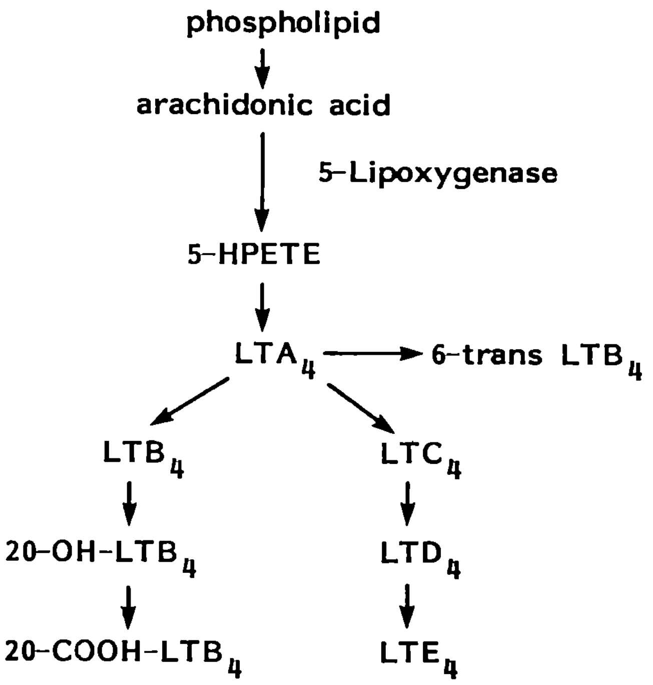


Figure 2 *5-Lipoxygenase metabolites in arachidonic acid cascade. LTB$_4$ and LTC$_4$ are enzymatically generated from LTA$_4$ by LTA$_4$ hydrolase and LTC$_4$ synthetase (GSH S-transferase).* 6-Trans *LTB$_4$ is a non-enzymatic metabolite of LTA$_4$. LTB$_4$ is metabolized by the ω-oxidation system to 20-OH-LTB$_4$ and 20-COOH-LTB$_4$ (ω-oxidates of LTB$_4$). GSH, glutathione, 5-HPETE, 5-hydroperoxyeicosatetraenoic acid*

It has been reported that LTC$_4$ production by eosinophils is 15 times higher than that by neutrophils[20]. However, the postoperative reduction in LTC$_4$ production does not seem to be caused by a reduced amount of contamination by eosinophils in the postoperative neutrophil preparations, as analysis of the neutrophil preparations with Giemsa staining did not demonstrate any perioperative difference in the percentage of eosinophils.

El-Maallem *et al.* observed that the cause of the postoperative decrement of neutrophil functions was a change in neutrophil subpopulation[6]. In the present study, we also observed an increased number and proportion of immature neutrophils in the postoperative peripheral circulation (*Table 1*). Several studies have demonstrated the correlation between neutrophil maturation and functional potency[25–27]. Therefore, the results in the present study, such as the impaired neutrophil capacity for superoxide production and the altered leukotriene metabolism may be, at least in part, attributable to the postoperative change in immature neutrophil proportion.

Stanley *et al.* noted decrements in neutrophil chemotaxis and random migration in patients who received general anaesthesia with inhalation agents[2]. In addition to such agents[2,28], several drugs such as catecholamine[29] and glucocorticoids[30,31] are known to depress neutrophil function. As patients who undergo major surgery cannot be free from surgical stress, higher plasma levels of catecholamine and glucocorticoid are occasionally observed.

We investigated whether materials exerting such an effect, including those agents mentioned above, were present in the postoperative plasma. In our experiment, neutrophils prepared from healthy volunteers were initially pre-incubated with plasma from patients before and after operation. The leukotriene-producing capacity was then analysed: however, no significant alteration was observed (data not shown).

In newborn infants[32], and in patients who suffer from chronic granulomatous disease[7,8] or diabetes mellitus[33,34], the superoxide-producing capacity of neutrophil is known to be low compared with that of healthy adults. This neutrophil dysfunction may attribute to the well-known high risk of bacterial infection in these cases. Similarly, patients who undergo major surgery may be at higher risk of bacterial infection because of the lower capacity for superoxide production by the neutrophils.

References

1. van Dijk WC, Verbrugh HA, Rijswijk REN, Vos A, Verhoef J. Neutrophil function, serum opsonic activity, and delayed hypersensitivity in surgical patients. *Surgery* 1982; **92**: 21–9
2. Stanley TH, Hill GE, Portas MR, Hogan NA, Hill HR. Neutrophil chemotaxis during and after general anesthesia and operation. *Anesth Analg* 1976; **55**. 668–73.
3. Duignan JP, Collins PB, Johnson AH, Bouchier-Hayes D. The association of impaired neutrophil chemotaxis with postoperative surgical sepsis. *Br J Surg* 1986; **73**: 238–40.
4. Cullen BF, Hume RB, Chretien PB Phagocytosis during general anesthesia in man. *Anesth Analg* 1975; **54**· 501–4
5. Davies JM, Sheppard K, Fletcher J The effect of surgery on the activity of neutrophil granule proteins. *Br J Haematol* 1983; **53**· 5–13.
6. El-Maallem H, Fletcher J. Effects of surgery on neutrophil granulocyte function. *Infect Immun* 1981; **32**: 38–41.
7. Quie PG, White JG, Holmes B, Good RA In vitro bactericidal function of human polymorphonuclear leukocytes Diminished activity in chronic granulomatous disease of childhood. *J Clin Invest* 1967; **46**: 668–79.
8. Curnutte JT, Kipnes RS, Babior BM. Defect in pyridine nucleotide dependent superoxide production by a particulate fraction from the granulocytes of patients with chronic granulomatous disease. *New Engl J Med* 1975; **293**: 628–32.
9. Ford-Hutchinson AW, Bray MA, Doig MV, Shipley ME, Smith MJH Leukotriene B, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. *Nature, Lond.* 1980; **286**: 264–5.
10. Goetzel EJ, Pickett WC. Novel structural determinants of the human neutrophil chemotactic activity of leukotriene B. *J Exp Med* 1981, **153**· 482–7.
11. Rola-Pleszczynski M, Gagnon L, Sirois P. Leukotriene B_4 augments human natural cytotoxic cell activity. *Biochem Biophys Res Commun* 1983; **113**: 531–7.
12. Johnson HM, Torres BA. Leukotrienes: positive signals for regulation of gamma-interferon production. *J Immunol* 1984; **132**: 413–16
13. Pech M, Piper PJ, Williams TJ. The effect of leukotrienes C_4 and D_4 on the microvascular of guinea-pig skin *Prostaglandins* 1981, **21**: 315–21.
14. Hedqvist P, Dahlen SE, Gustafsson L, Hammarstrom S, Samuelsson B. Biological profile of leukotrienes C_4 and D_4. *Acta Physiol Scand* 1980; **110**: 331–3.
15. Böyum A. Isolation of lymphocytes, granulocytes, and macrophages. *Scand J Immunol* 1976; **5** (Suppl 5): 9–15.
16. Newburger PE, Chovaniec ME, Cohen HJ. Activity and activation of granulocyte superoxide-generating system. *Blood* 1980; **55**: 85–92.
17. Salari H, Braquet P, Naccache P, Borgeat P. Characterization of effect of *N*-formyl-methionyl-leucyl-phenylalanine on leukotriene synthesis in human polymorphonuclear leukocytes. *Inflammation* 1985; **9**· 127–38.
18. Hamasaki T. Quantitative determination of arachidonate 5-lipoxygenase metabolites in human polymorphonuclear leukocytes by reverse-phase high-performance liquid chromatography. *Hiroshima J Med Sci* 1986; **35**: 99–105
19. McCool SR, Betts WH, Murphy GA, Cleland LG. Determination of 5-lipoxygenase activity in human polymorphonuclear leukocyte using high-performance liquid chromatography *J. Chromatogr* 1986; **378**: 444–9.
20. Poubelle P, Beaulieu AD, Nedeau M, Laviolette M, Borgeat P. The metabolism of arachidonic acid through the lipoxygenase pathways in human phagocytes. In. Otterness I, Lewis A, Capetole R, eds. *Advances in Inflammation Research, Vol 11* New York: Raven Press, 1986: 17–29.
21. Cochrane CG. The enhancement of inflammatory injury *Am Rev Respir Dis* 1987; **136**: 1–2.
22. Samuelsson B Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science, N.Y.* 1983, **220**: 568–75.
23. Radmark O, Shimizu T, Jornvall H, Samuelsson B. Leukotriene A_4 hydrolase in human leukocytes, purification and properties. *J Biol Chem* 1984, **259**: 12339–12345.
24. Bach MK, Brashler JR, Morton DR. Solubilization and characterization of the leukotriene C_4 synthetase of rat basophil leukemia cells. *Arch Biochem Biophys* 1984, **230**. 455–65.
25. Berkow RL, Dodson RW. Purification and functional evaluation of mature neutrophils from human bone marrow. *Blood* 1986; **68**: 853–60.
26. Glasser L, Fiederlein RL. Functional differentiation of normal human neutrophil. *Blood* 1987; **69**. 937–44.
27. Zimmerman JJ, Shelhamer JH, Parrillo JE. Quantitative analysis of polymorphonuclear leukocyte superoxide anion generation in critically ill children. *Crit Care Med* 1985, **13**: 143–50.
28. Bruce DL. Effect of halothane anesthesia on experimental salmonella peritonitis in mice. *J Surg Res* 1967; **7**: 180–5.
29. Hill HR, Estensen RD, Quie PG *et al* Modulation of human neutrophil chemotactic responses by cyclic 3′,5′-guanosine monophosphate and cyclic 3′,5′-adenosine monophosphate. *Metabolism* 1975; **24**: 447–56.
30. Goldstein IM, Roos D, Weissmann G, Kaplan HB Influence of corticosteroids on human polymorphonuclear leukocyte function in vitro *Inflammation* 1976; **1**: 305–15.
31. Tennenberg SD, Bailey WW, Cotta LA, Brodt JK, Solomkin JS. The effect of methylprednisolone on complement-mediated neutrophil activation during cardiopulmonary bypass. *Surgery* 1986; **100**: 134–41.
32. Davies PA, Gothefors LA *Bacterial Infections in the Fetus and Newborn Infant*. Philadelphia: W B. Saunders Co., 1984
33. Mowat AG, Baum J Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. *New Engl J Med* 1971; **284**: 621–7.
34. Casey JJ Host defense and infections in diabetes mellitus. In· Ellenberg M, Rifkin H, eds. *Diabetes Mellitus—Theory and Practice.* New York: Medical Examination Pubs, 1983: 667–78

Paper accepted 28 January 1988

Br. J. Surg. 1988, Vol. 75, July,
686–689

Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery

**M. R. Lassen,
L. C. Borris,
H. M. Christiansen,
F. Møller-Larsen*,
V. E. Knudsen*,
P. Boris†, A.-M. Nehen†,
A. de Carvalho‡, A.-G. Jurik‡, B. W. Nielsen*
and U. Lucht***

*Departments of Orthopaedics and †Diagnostic Radiology, Aalborg Hospital, Aalborg, and Departments of *Orthopaedics and ‡Diagnostic Radiology, Aarhus Municipal Hospital, Aarhus, Denmark*

Correspondence to.
Dr M. R Lassen, Filippavej 27,
DK-9000 Aalborg, Denmark

In a prospective, double-blind controlled study we have compared the prophylactic efficacy against deep vein thrombosis of low-dose heparin + dihydroergotamine (A), low molecular weight heparin + dihydroergotamine (B) and placebo (C). A total of three hundred and fifty-six patients undergoing total hip replacement were randomized into three groups and 316 patients were analysed. All thrombi were verified by ascending phlebography. One-third of the patients developed deep vein thrombosis in group A and B, differing significantly from group C. The operative blood loss in group B was higher than that in groups A and C. However, the number of patients transfused and their transfusion requirements did not differ. Severe bleeding occurred in one patient in each group. No deaths were registered during the study. Our study indicates that prophylactic treatment against postoperative deep vein thrombosis with low molecular weight heparin + dihydroergotamine once daily is as effective and safe as conventional low-dose heparin + dihydroergotamine twice daily in patients undergoing total hip replacement. The once-daily regimen has the advantage of better patient acceptance and less nursing time.

Keywords: Heparin, low molecular weight heparin, deep vein thrombosis, dihydroergotamine, total hip replacement, ascending phlebography, haemorrhage

Patients undergoing total hip replacement have a high risk of venous thrombosis and thromboembolic complications. Without prophylaxis, an incidence of postoperative deep vein thrombosis of between 45 and 70 per cent has been reported[1], and in a large series the incidence of fatal pulmonary embolism was 2·3 per cent[2]. Prophylaxis with low doses of heparin is effective in most types of surgery, but has insufficient antithrombotic potency in patients undergoing total hip replacement[3–6]. When heparin is combined with dihydroergotamine the incidence of thrombosis is reduced in these high-risk patients[5,7–9]. Only one of these studies, however, included a group of untreated patients for comparison.

Low molecular weight heparin (LMWH) has now been introduced as a prophylactic alternative. In experimental studies it has had more antithrombotic potency and less risk of haemorrhagic complications than conventional heparin[10,11]. Furthermore, LMWH has the clinical advantage that it can be administered as a single daily dose.

The present prospective, randomized, double-blind study compares the antithrombotic efficacy and safety of low-dose heparin + dihydroergotamine (LDH/DHE) and low molecular weight heparin + dihydroergotamine (LMWH/DHE) and placebo in patients undergoing total hip replacement.

Patients and methods

The study took place during a 2-year period from November 1984 at Aalborg Hospital and Aarhus Municipal Hospital, Denmark. All patients aged 40 years and over who underwent total hip replacement entered the study, but were excluded if any of the following features were present: treatment with anticoagulants, myocardial infarction within the past 6 months, coronary insufficiency with angina at rest, severe hypertension (diastolic pressure > 120 mmHg), impaired renal or hepatic function, sepsis and/or shock, haemorrhagic diathesis, peripheral arterial disease, post-thrombotic syndrome, treatment with non-steroidal anti-inflammatory drugs or acetylsalicylic acid, and hypersensitivity to heparin, ergotamine, trypsin or radio-opaque dye.

The study was approved by The National Health Service of Denmark and the local ethical committees. A total of 356 patients were included and gave informed consent. During the study 40 patients in whom the protocol had not been correctly followed were excluded and 316 patients completed the study (*Table 1*). All operations were performed through a posterolateral approach. According to the routine of the departments, all patients below 60 years of age received a cementless prosthesis (56 patients) and those aged 60 or over a cemented prosthesis (260 patients). There was no difference between the groups according to sex, age, anaesthesia, duration of operation (*Table 2*), and risk factors (varicose veins, previous thromboembolic events).

Heparin preparations

Dihydergot-Heparin 5000®. Five thousand units of sodium heparin (APTT activity = anti-Xa activity), average molecular weight = 15 000 in a fixed combination with 0·5 mg dihydroergotamine-mesylate (total volume 0·7 ml).

Heparin-NM-Dihydergot®. Fifteen hundred units APTT of low molecular weight heparin (6000 units anti-Xa), average molecular

Table 1 *Reasons for exclusion*

	A	B	C	Total
Allocated	122	118	116	356
Excluded				
Informed consent withdrawn	2	5	5	12
Operation cancelled	3	0	5	8
Phlebography not performed	1	2	3	6
Miscellaneous	4	4	6	14
Analysed	112	107	97	316

Treatments: A, low-dose heparin + dihydroergotamine; B, low molecular weight heparin + dihydroergotamine, C, placebo

0007–1323/88/070686–04$3 00 © 1988 Butterworth & Co (Publishers) Ltd

Table 2 *Patient characteristics*

	A (n=112)	B (n=107)	C (n=97)
Sex M:F	50:62	55:52	41:56
Age (years)			
Median	69	69	69
Range	43–83	48–87	40–88
Anaesthesia			
general:epidural	101:11	95:12	92:5
Duration of operation (min)			
Median	114	114	110
Range	45–275	50–230	60–210

Treatment: A, low-dose heparin + dihydroergotamine; B, low molecular weight heparin + dihydroergotamine; C, placebo

weight = 7600 in a fixed combination with 0·5 mg dihydroergotamine-mesylate (total volume 0·5 ml).

Prophylaxis

The patients were allocated by random numbers to injections of LDH/DHE twice daily (group A), or injections of LMWH/DHE once daily (morning) and placebo (isotonic saline) once daily (evening, group B), or injections of placebo (isotonic saline) twice daily (group C). The injections were given subcutaneously in the abdominal wall and were started 2 h pre-operatively and continued for 7 days.

Before this trial was instituted, none of the participating departments had been using any thromboprophylactic methods other than antithromboembolic physiotherapy and early mobilization (on the fourth postoperative day), both of which were continued during the trial.

Correct prophylaxis was given to 294 patients (100 patients in group A and 97 in groups B and C respectively). Correct prophylaxis was defined as administration in correct order of all doses until at least 12 injections had been given postoperatively or a thromboembolic complication occurred.

Diagnosis of deep vein thrombosis

On the fifth day after surgery all patients were examined by ^{99m}Tc-plasmin scanning (sensitivity = 0·94 and specificity = 0·56), according to Olsson *et al.*[12]. Examination was performed with a collimated NaI-scintillation detector (Lysotec, NOVO A/S, Denmark).

Positive scannings were confirmed by ascending phlebography on the isotopically positive leg on the following day. Phlebography was performed using the method described by Rabinov and Paulin[13] and Zachrisson and Jansen[14]. At each centre two radiologists performed all the radiographic examinations and interpreted all the venograms. The contrast medium used was Iohexol (Omnipaque 240, Nyegaard and Co. A/S, Oslo, Norway).

Treatment of deep vein thrombosis

In the case of phlebographically verified thrombosis, prophylaxis was discontinued and the patient started treatment with heparin followed by a vitamin K antagonist for 3 months.

Registration of complications

The clinical course of each patient was followed until discharge from hospital, apart from this, no specific examinations to detect pulmonary embolism were carried out. Blood loss during the operation was estimated by the anaesthetist from the amount of blood in suction bottles and swabs. Postoperative blood loss was measured. Blood transfusions, formation of haematomas and reoperations were recorded (all operation wounds were inspected on the fourth postoperative day by the surgeons) Allergic side-effects, as well as local complications at the injection sites, were registered.

Statistics

The results were evaluated statistically using the χ^2 test and Mann–Whitney U test with significance level of $P < 0{\cdot}05$ The comparisons between the treatment groups were based on 316 patients, except when stated otherwise.

Results

No deaths and no clinical evidence of pulmonary embolism were registered during the course of the study. Of 316 patients, 122 developed deep vein thrombosis (92 in the operated leg and 30 in the contralateral leg). The incidence of deep vein thrombosis was 30 per cent in group A, 33 per cent in group B and 55 per cent in group C. The incidence of deep vein thrombosis in groups A and B was significantly reduced when compared with group C ($P < 0{\cdot}01$), but there was no significant difference between group A and group B. When the analysis was based on the 294 patients with correct prophylaxis the incidence of deep vein thrombosis in group A and B was 29 per cent and 32 per cent respectively; this did not alter the outcome. Significantly fewer patients in group B had thrombosis located in the femoropopliteal segments than in group C ($P < 0{\cdot}01$). The number of patients with isolated thrombosis in the crural segment was significantly lower in group A than in group C ($P < 0{\cdot}01$). Fewer patients with verified thrombosis in group B had a thrombus located in the femoropopliteal segment compared with patients with thrombosis in group A ($P < 0{\cdot}05$) (*Table 3*).

The operative blood loss of patients in group B did not differ from that in group A (*Table 4*), but was significantly higher than that in group C ($P < 0{\cdot}05$). In the 294 patients given correct prophylaxis the operative blood loss in group B was even higher and differed significantly from that in both of the other groups. Postoperative blood loss, number of patients transfused and the amount of blood transfused did not differ between the groups. In group A excessive bleeding during the operation was observed in one patient, who lost 5800 ml of blood because of an unintentional arterial injury. Consequently the operation lasted 225 min. Although prophylaxis was continued the postoperative blood loss did not exceed the average observed in the group. One patient in group C underwent evacuation of a wound haematoma 9 days after the primary operation. Two patients were excluded from further analysis, one in group B developed gastrointestinal bleeding (gastric ulcer), and another in group C developed subarachnoid bleeding from rupture of a basilar artery aneurysm 3 days after surgery. Both patients were transferred to other departments which made examination for deep vein thrombosis impossible. In no other patient were severe bleeding complications observed; no surgical intervention due to bleeding was necessary. Haematoma at the injection sites was observed in 42 patients in group A, in 33

Table 3 *Distribution of 122 patients with deep vein thrombosis according to location of the most proximally observed thrombosis*

	A	B	C	Total
Location				
Femoropopliteal segments	21	13	28	62
Crural segment	13	22	25	60
Total	34	35	53	122

Treatments. A, low dose heparin + dihydroergotamine; B, low molecular weight heparin + dihydroergotamine; C, placebo

Table 4 *Data on bleeding*

	A (n=112)	B (n=107)	C (n=97)
Operative blood loss (ml)			
Median	627·5	700	650
Upper and lower quartile	500, 900	500, 1300	400, 850
Postoperative blood loss (ml)			
Median	462·5	430	455
Upper and lower quartile	170, 700	200; 650	180; 625
No. of patients transfused	98	96	86
Blood transfused (ml)			
Median	812·5	997·5	772·5
Upper and lower quartile	556; 1170	582·5; 1500	605, 1000

Treatments· A, low dose heparin + dihydroergotamine; B, low molecular weight heparin + dihydroergotamine patients in group B and in 12 patients in group C. No other side-effect related to the medication was observed.

Discussion

In the present study we found the antithrombotic efficacy of LDH/DHE comparable to that in previous studies on patients undergoing total hip replacement[7,15]. Moreover we found that LMWH/DHE in these patients was equally protective against deep vein thrombosis, which is similar to the results obtained in general surgery[16–19].

Treatment with LMWH/DHE in our patients reduced the incidence of postoperative deep vein thrombosis from 55 per cent to 33 per cent. A recently published, controlled study by Turpie *et al.*[20] obtained an even higher reduction (51·3 to 10·8 per cent). The patients were treated with LMWH (2400 units anti-Xa twice daily) without the addition of DHE, starting from 12 to 24 h after surgery. The higher efficacy of LMWH may be explained by the difference in the time at which the phlebography was performed. In our study all phlebographic examinations were made on the sixth day after surgery, whereas the phlebography in Turpie's study was done on the 14th postoperative day in a number of patients. Thrombus formation starts during surgery, reaches a maximum on the first day and ceases about the fifth postoperative day[7,21], after which fibrinolysis is restored and the thrombi start to be dissolved. As heparin restricts thrombus formation, lysis is facilitated in patients treated with heparin. Thus, more thrombi can be detected on the sixth day after surgery than when phlebography is delayed.

It is generally accepted that thrombi which develop in the proximal venous segments of the leg are more liable to cause fatal embolic complications. Treatment with LMWH/DHE was more effective than LDH/DHE in reducing the number of thrombi in the femoropopliteal segments in our patients. The clinical value of this finding, however, may be limited, because the extension of the thrombi may change, due to the fact that it is impossible to tell whether the thrombus is actually growing or being dissolved at the time of diagnosis. The important information is the overall reduction in the incidence of postoperative deep vein thrombosis.

In this study patients treated with LMWH/DHE had a higher operative blood loss than the other patients. LMWH has a greatly increased bioavailability compared with conventional heparin, partly because of different absorption characteristics[22]. Thus, the interval of 2 h between the injection and the operation may have been too short, so that the maximum effect of LMWH was reached during surgery. Instead of giving a fixed dosage of LMWH it would probably be preferable to vary the dose according to body weight.

The safety of prophylaxis with drugs that influence haemostatis is traditionally evaluated from the number of patients who develop excessive bleeding or wound haematomas during the course of treatment. The very low rate of haemorrhagic complications in this study, compared with previously reported frequencies, was partly due to the fact that no wound haematomas developed in patients treated with heparin. We are aware that wound haematomas of minor clinical importance may have escaped registration because it was the surgeons who inspected the wounds.

Haematoma at the injection sites, which we observed in 75 patients treated with LDH or LMWH, is a well-known side-effect when heparin is injected subcutaneously. In rare instances these haematomas may reach a considerable size[15]. All haematomas in our patients were small and caused no discomfort.

We observed none of the serious vasospastic or cardiac complications which have been ascribed to treatment with dihydroergotamine[23,24].

Our study indicates that prophylactic treatment against postoperative deep vein thrombosis with LMWH/DHE once daily is as effective and safe as conventional LDH/DHE twice daily in patients undergoing total hip replacement. The once-daily regimen has the advantage of better patient acceptance and less nursing time.

Acknowledgements

We thank Dr P. Rødbro and the technicians of the Department of Clinical Physiology, Aalborg Hospital, and Dr H. Hansen and the technicians of the department of Nuclear Medicine, Aarhus Municipal Hospital, for help with the plasmin scannings. We are indebted to Sandoz A/S, Denmark, for supplying the heparin.

References

1. Leyvraz PF, Richard J, Bachmann F *et al.* Adjusted *versus* fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *New Engl J Med* 1983; **309**. 954–8.
2. Johnson R, Green JR, Charnley J. Pulmonary embolism and its prophylaxis following the Charnley total hip replacement. *Clin Orthop* 1976, **127**· 123–32.
3. Hampson WGJ, Harris FC, Lucas HK *et al.* Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. *Lancet* 1974; **ii**: 795–7.
4. Harris WH, Salzman EW, Athanasoulis C *et al.* Comparison of warfarin, low-molecular-weight dextran, aspirin and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. *J Bone Joint Surg* 1974; **56A**: 1552–62.
5. Kakkar VV, Stamatakis JD, Bentley PG *et al.* Prophylaxis for postoperative deep-vein thrombosis· Synergistic effect of heparin and dihydroergotamine. *JAMA* 1979; **241**: 39–42.
6. Sikorski JM, Hampson WG, Staddon GE. The natural history of aetiology of deep vein thrombosis after total hip replacement. *J Bone Joint Surg* 1981; **63B**: 171–7.
7. Sagar S, Stamatakis JD, Higgins AF *et al.* Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. *Lancet* 1976; **i**: 1151–4
8. Tscherne H, Westermann K, Trentz O *et al.* Thromboembolische Komplikationen und ihre Prophylaxe beim Huftgelenksersatz. *Unfallheilkunde* 1978; **81**: 178–87.
9. Schöndorf TH, Weber U. Prevention of deep vein thrombosis in orthopedic surgery with the combination of low dose heparin plus either dihydroergotamine or dextran. *Scand J Haemat* 1980; Suppl. **36**: 126–40.
10. Esquivel CO, Bergqvist D, Björck CG *et al.* Comparison between commercial heparin, low-molecular weight heparin and pentosan polysulphate on hemostatis and platelets *in vivo*. *Thromb Res* 1982; **28**: 389–99.
11. Persson E, Nordenstrom J, Nilsson-Ehle P *et al.* Lipolytic and anticoagulant activities of a low molecular weight fragment of heparin. *Eur J Clin Invest* 1985; **15**: 215–20.
12. Olsson CG, Albrechtsson U, Darte L *et al.* Tc-99m plasmin for rapid detection of deep vein thrombosis. *Nucl Med Commun* 1982; **3**: 41–52.
13. Rabinov K, Paulin S. Roentgendiagnosis of venous thrombosis in the leg. *Arch Surg* 1972; **104**. 134–44.
14. Zachrisson BE, Jansen H. Phlebographic signs in fresh postoperative venous thrombosis of the lower extremity. *Acta Radiol* (*Diagn*) 1973; **14**: 82–96.
15. Fredin HO, Rosberg B, Arborelius Jr M *et al* On thromboembolism after total hip replacement in epidural analgesia: a controlled study of dextran 70 and low-dose heparin combined with dihydroergotamine. *Br J Surg* 1984; **71**: 58–60.
16. Kakkar VV, Djazaeri B, Fok J *et al.* Low-molecular-weight heparin and prevention of postoperative deep vein thrombosis. *Br Med J* 1982; **284**· 375–9.
17. Kakkar VV, Murray WJG. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism· a co-operative study. *Br J Surg* 1985; **72**· 786–91
18. Bergqvist D, Burmark US, Frisell J *et al.* Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg* 1986; **73**: 204–8.
19. Sasahara AA, Koppenhagen K, Häring R *et al.* Low molecular weight heparin plus dihydroergotamine for prophylaxis of

postoperative deep vein thrombosis. *Br J Surg* 1986; **73**: 697–700
20. Turpie AGG, Levine MN, Hirsh J *et al.* A randomized controlled trial of a low-molecular-weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986; **315**: 925–9.
21. Westermann K, Trentz O, Pretschner P *et al.* Thromboembolism after hip surgery. *Int Orthop* 1981, **4**. 253–7.
22. Dawes J, Bara L, Billaud E *et al.* Relationship between biological activity and concentration of a low-molecular-weight heparin (PK 10169) and unfractionated heparin after intravenous and subcutaneous administration. *Haemostatis* 1986; **16**: 116–22.
23. Kniemeyer HW, Sandmann W, Winter J *et al.* Spastische Gefassreaktion nach Dihydroergotamin—Komplikation der postoperativen Thromboembolieprophylaxe. *Aktuelle Chirurgie, Stuttgart* 1983; **18**: 199–206.
24. Ekeström S, Liljeqvist L, Nordhus O Negative effects of dihydroergotamine (Orstranorm) on central haemodynamics and aorto-coronary bypass blood flow. *Scand J Thorac Cardiovasc Surg* 1985; **19**: 77–83.

Paper accepted 6 February 1988

Surgical workshop

Br. J. Surg. 1988, Vol. 75, July, 689

An operation for incisional hernia

F. E. Weale

Gravesend and North Kent Hospital, Gravesend, Kent, UK
Correspondence to: Mr F. E Weale

The problem of incisional hernia is not solved. Recurrence rates are not insignificant and the variety of operations designed to deal with it reflects uncertainty regarding the best method. In large hernias muscle retraction needs to be overcome. Operation should be confined to those patients who have successfully dieted if obese.

Method

The abdomen is disinfected with iodine and spirit. The skin of the hernia is incised along the whole length of the scar. Opening the peritoneum is avoided if possible. The skin and subcutaneous fat are reflected from the underlying peritoneum on either side until the edges of the abdominal musculature are encountered by palpation. They are then cleared of overlying fat and underlying peritoneum for 3 to 4 cm.

On each side a piece of tubing, as from a large Redivac drain (O.E.C. Ltd., UK), is introduced through the skin at one end of the wound in line with the cleared muscle bellies so as to lie on them, and brought out through the skin at the other end. For drainage the tubing is longitudinally incised half way along its length. Where it projects through the skin its ends are secured with safety pins (*Figure 1*).

Six to eight strong extraperitoneal interrupted Vicryl (Ethicon Ltd, UK) sutures are inserted through the musculature to surround the tubing. They are left untied until they are all in position. Considerable force can then be exerted to bring the muscles together, after which the sutures are tied. The apposed muscle edges are lightly stitched together. Peritoneal defects are ignored. The subcutaneous dead space is reduced by skin excision, drained and closed.

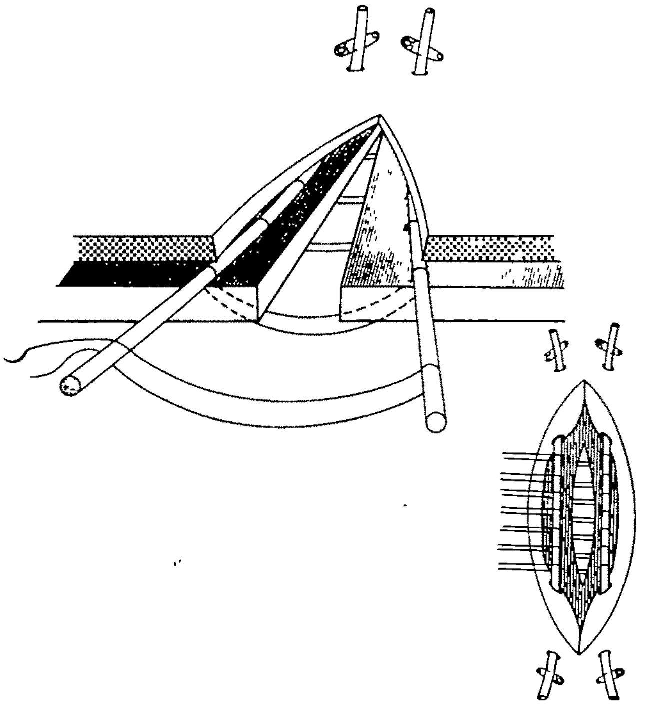


Figure 1 *Method of repair of incisional hernia*

The patient can be discharged from hospital after about 10 days. A district nurse must regularly dress the emergent tubes from which drainage continues as long as they are in place. A month or so after the operation the tubes are tested for looseness in their respective tracks, indicating both the relaxation of the grip due to the sutures, and the satisfactory healing of the muscles in an apposed position. The tubes are withdrawn on the application of a disinfectant. Thereafter dressings are applied to the exit wounds until all discharge ceases.

Five of six patients have had this operation with satisfactory results after two years. One patient, in whom nylon sutures were used instead of Vicryl, suffered a minor recurrence, and one of his nylon sutures was extruded.

This procedure is designed to avoid sutures which, under tension, cut through tissues. The risk of infection from synthetic material or its late extrusion is eliminated.

Paper accepted 24 January 1988

0007-1323/88/070689-01$3 00

Br. J. Surg. 1988, Vol. 75, July, 690–692

Oxygen consumption following trauma: a reappraisal in severely injured patients requiring mechanical ventilation

J. D. Edwards, A. D. Redmond, P. Nightingale and R. G. Wilkins

Intensive Care Unit and Accident and Emergency Department, University Hospital of South Manchester, Withington, Manchester M20 8LR, UK

Correspondence to:
Dr J. D. Edwards

Oxygen consumption (V_{O_2}) immediately following major injury in man has been said to be reduced. The evidence for this is poor. We have therefore measured V_{O_2} soon after major injury in 16 patients. V_{O_2} was reduced in only two patients, within the normal range in four and increased in ten. V_{O_2} was maintained by increased oxygen extraction in six patients leading to low levels of mixed venous oxygen saturation. There is no evidence for an 'ebb phase' response in man.

Keywords: Trauma, oxygen consumption, ebb phase, flow phase, oxygen delivery

For four decades the metabolic response to trauma in man has been regarded as divided into two phases. It has been said that there is an initial phase of low oxygen consumption lasting up to 48 h—the 'ebb phase'—followed by a period of high oxygen consumption and tissue repair—the 'flow phase'[1]. This hypothesis has been widely promulgated and extensively quoted[2–5] thus achieving the status of dogma. It is, however, based almost entirely on one study of a small number of poorly selected patients using methods notoriously prone to error and with poor interpretation of the results. Indeed recent reviews[6,7] have commented on the paucity of clinical studies in man, as opposed to experimental studies on laboratory animals, which have demonstrated an ebb phase response after injury. They also comment on the unconvincing nature of the small amount of evidence that is available. In early studies oxygen consumption was calculated from measurements of the oxygen content and volume of inspired and expired gases. Using this method, combined with measurements of arterial and mixed venous oxygen content, Fick calculated cardiac output using the equation which now bears his name:

$$\mathrm{CO} = \frac{V_{O_2}}{C_{aO_2} - C_{\bar{v}O_2}}$$

where CO = cardiac output, C_{aO_2} = arterial oxygen content, $C_{\bar{v}O_2}$ = mixed venous oxygen content and V_{O_2} = oxygen consumption. It is now possible to measure cardiac output accurately and with reproducible results at the bedside using the thermodilution technique[8]. An alternative form of the Fick equation can be used to calculate V_{O_2}. Using this alternative form of the Fick equation (*see* methods section below) we have studied prospectively the V_{O_2} in 16 patients soon after receiving major blunt trauma, all of whom required mechanical ventilation. This alternative method is considered more accurate than the original method, especially in patients requiring mechanical ventilation with supplemental inspired oxygen[9]. As V_{O_2} is now known to correlate with survival in shocked and critically ill patients it is now routinely measured in modern intensive care units[10–12].

Patients and methods

The clinical details of the patients and their injuries are summarized in *Table 1*.

All patients were managed on the Intensive Care Unit (ICU) of the University Hospital of South Manchester. The ambient temperature of this unit is maintained at 24°C. Immediately after arrival at hospital the trauma score was calculated by at least one of the authors. Injury severity score was calculated at death or on discharge from hospital. General resuscitation and fluid replacement was initiated in the Accident and Emergency Department and this was continued during transfer to, and for the period on, the ICU. All patients received a gelatin solution and three required transfusions of uncrossmatched blood. All patients were mechanically ventilated and had arterial oxyhaemoglobin saturation maintained at ⩾95 per cent by adjustment of fractional inspired oxygen concentration (FI_{O_2}) and other ventilator settings. The FI_{O_2} required to achieve this varied from 0·5 to 1·0 with a mean of 0·65. The indications for mechanical ventilation were apnoea, clinical evidence of respiratory distress, inability of the patient to

Table 1 *Patient details*

Case number	Trauma score	Injury severity score	Age	Mode of injury	Outcome	Major fractures and some associated injuries
1	14	25	57	RTA	Survived	MRF, pneumothoraces
2	8	34	66	Fall	Died	MRF, skull and long bones
3	8	34	17	RTA	Survived	MRF, facial and long bones
4	6	32	56	Assault	Survived	MRF, facial and long bones
5	7	32	18	RTA	Survived	Degloving injury and amputation of leg
6	8	32	27	RTA	Survived	MRF, skull and long bones
7	9	24	22	RTA	Survived	MRF, long bones
8	7	66	21	RTA	Died	MRF, skull and long bones
9	9	38	32	RTA	Survived	MRF, skull and long bones
10	8	48	23	RTA	Survived	MRF, facial and long bones
11	8	48	17	RTA	Survived	MRF and lumbar spine; ruptured spleen
12	8	43	34	RTA	Survived	MRF and long bones; perforated jejunum
13	9	32	57	RTA	Died	MRF and long bones, amputation of arm
14	6	34	19	RTA	Survived	Long bones. Head injury; pulmonary contusion
15	15	41	42	RTA	Died	Pelvis and long bones; perforated large bowel
16	11	16	69	Fall	Survived	MRF and long bones

RTA, road traffic accident; MRF, multiple rib fractures maintain protective airway reflexes or hypoxaemia resistant to supplemental inspired oxygen. All patients had a pulmonary artery flotation catheter and a femoral arterial line inserted as part of their routine monitoring.

Cardiac output was determined by a standard thermodilution technique using cooled injectate and an in-line temperature probe with display of the thermodilution curve The mean of three measurements within 5 per cent of each other was taken[12]. From samples of blood taken from the femoral and pulmonary arteries, haemoglobin content and oxygen saturation were measured and oxygen contents were calculated using the following formulae:

$$C_{aO_2} = (\text{Hb} \times \text{saturation} \times 1{\cdot}39) + \text{dissolved } O_2$$

$$C_{\bar{v}O_2} = (\text{Hb} \times \text{saturation} \times 1{\cdot}39) + \text{dissolved } O_2$$

Cardiac output was indexed for body surface area, derived from standard nomograms based on measurements of the patients' height and weight. Oxygen delivery and consumption were calculated from the formulae:

$$D_{O_2} = \text{CI} \times 10 \times C_{aO_2} \text{ml min}^{-1} \text{m}^{-2}$$

$$V_{O_2} = \text{CI} \times 10 \times (C_{aO_2} - C_{\bar{v}O_2}) \text{ ml min}^{-1} \text{m}^{-2}$$

where CI = cardiac index in litres min^{-1} m^{-2} and D_{O_2} = oxygen delivery.

The oxygen extraction ratio (OER) was determined from the formula:

$$\text{OER} = \frac{C_{aO_2} - C_{\bar{v}O_2}}{C_{aO_2}}$$

A record of mixed venous oxyhaemoglobin saturation ($S_{\bar{v}O_2}$) was made.

No patient received inhalational anaesthesia or surgery before the measurements were made. Analgesia was provided with papaveretum 15–30 mg intravenously as required.

The mean time from injury to haemodynamic measurements being made was 1·6 h (range 0·8–9 h).

Results

The values of CI, C_{aO_2}, D_{O_2}, V_{O_2}, OER and $S_{\bar{v}O_2}$ are shown in *Table 2* and in *Figures 1*, *2* and *3*.

In summary the V_{O_2} was higher in ten patients and within the normal range in four patients. In only two patients was V_{O_2} below normal; one of these (case 4) had a blood alcohol level of 356 mg per cent and in the other D_{O_2} was well below the level thought to be critical in man[13]. In seven patients V_{O_2} was maintained despite a low D_{O_2} by increases in OER, leading to low levels of $S_{\bar{v}O_2}$ in six patients.

The mean intrapulmonary shunt (Qs/Qt per cent) was 17·2 ± 7·3 with a range of 9–34 per cent.

Table 2 *Oxygen transport variables*

Case number	CI	C_{aO_2}	D_{O_2}	V_{O_2}	OER	$S_{\bar{v}O_2}$
1	5·8	14·5	841	145	17	92
2	2·7	13·0	351	119	34	71
3	3·5	18·2	637	155	24	79
4	4·4	14·8	651	105	16	87
5	5·5	18·5	1018	176	17	85
6	4·2	18·2	764	176	23	75
7	2·5	14·3	357	110	31	52
8	2·8	16·8	470	308	65	36
9	5·3	15·1	800	175	22	79
10	4·9	16·9	828	176	21	82
11	3·4	16·4	558	190	34	66
12	1·8	14·5	261	94	36	64
13	5·4	15·3	826	238	29	77
14	6·6	15·0	990	198	20	82
15	6·9	13·8	952	186	20	81
16	2·6	12·9	335	190	56	43

CI, cardiac index (litres min^{-1} m^{-2}); C_{aO_2}, arterial oxygen content (ml dl^{-1}); D_{O_2}, oxygen delivery index (ml min^{-1} m^{-2}); V_{O_2}, oxygen consumption index (ml min^{-1} m^{-2}); OER, oxygen extraction ratio per cent; $S_{\bar{v}O_2}$, mixed venous oxygen saturation per cent

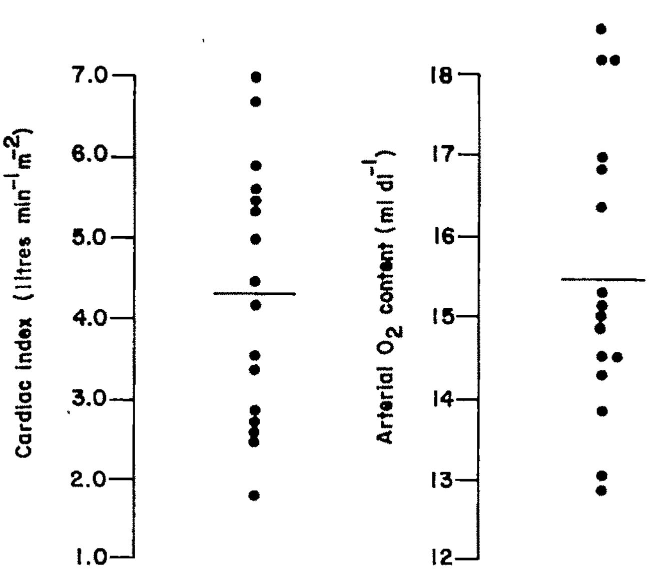


Figure 1 *Cardiac index and arterial oxygen content of 16 patients*

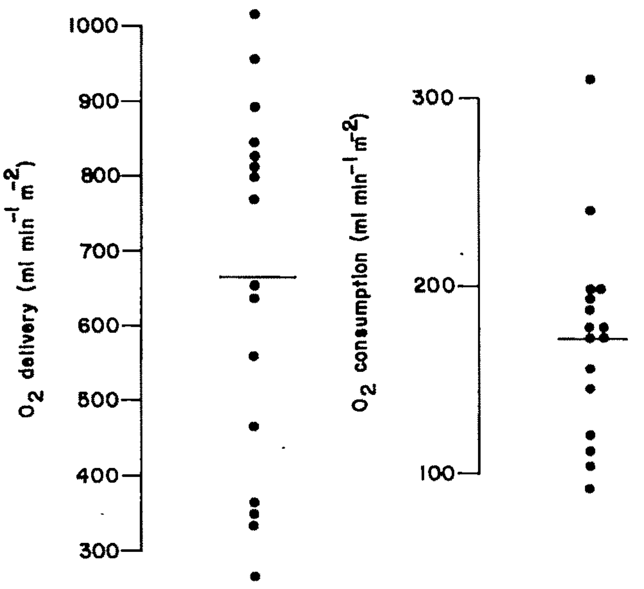


Figure 2 *Oxygen delivery and consumption of 16 patients*

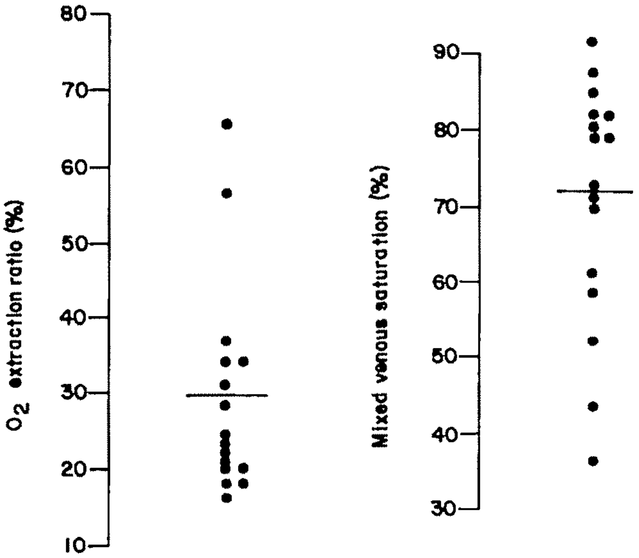


Figure 3 *Oxygen extraction ratio and mixed venous oxygen saturation of 16 patients*

Discussion

The occurrence of an 'ebb phase' after injury in man is an attractive hypothesis but cannot be supported by the evidence available. Cuthbertson[1] claimed to have demonstrated that V_{O_2} following injury in man was reduced for up to 48 h. He studied seven patients, three of whom had undergone elective orthopaedic procedures performed under spinal or general anaesthesia. The other four patients had relatively minor injuries with injury severity scores, calculated from the information provided, of 4, 4, 4, and 9 respectively. A review of his data reveals that in five patients the V_{O_2} on the first day of injury was higher than on subsequent days in the so-called flow phase.

Using a more accurate method in a larger group of patients with much more severe injuries we have found that V_{O_2} is not reduced after major trauma. Our findings are supported by those of Cournand *et al.*[14] who found low levels of $S_{\bar{v}O_2}$ and increased OER after injury before fluids, blood or oxygen had been administered. They studied 36 patients in an effort to determine the cause of post-traumatic shock. They did not calculate V_{O_2} but provided the data necessary to do so. Their results demonstrate that as shock became more severe OER increased, maintaining V_{O_2} at higher than normal levels but producing low levels of $S_{\bar{v}O_2}$. In a study aimed primarily at identification of variables associated with outcome after major trauma and haemorrhage, Shoemaker *et al.*[15] showed that V_{O_2} was lower in those ultimately destined to die but within the normal range in many. The low levels of V_{O_2} were associated with critically low levels of D_{O_2}. The values for $S_{\bar{v}O_2}$ are not given but mean values can be calculated from the information provided to be 57 per cent in survivors and 48 per cent in non-survivors, demonstrating increased OER with maintained V_{O_2} in the face of a reduced D_{O_2}.

Thus the true metabolic response to injury in man is the maintenance of a normal V_{O_2}, if necessary by increases in OER leading to low levels of $S_{\bar{v}O_2}$. In the absence of sepsis or established adult respiratory distress syndrome the $S_{\bar{v}O_2}$ is considered the best single indicator of tissue oxygen availability, low levels indicating reduced availability[16,17]. There is general agreement that $S_{\bar{v}O_2}$ levels of 60 per cent or less are associated with tissue hypoxia and that levels approaching 40 per cent are critical and not compatible with survival if sustained[18].

Stoner[7] has recently reviewed the metabolic effects of trauma and has commented on the paucity of evidence for an ebb phase response in man and the difference between the response of small laboratory animals and that of larger mammals. He has also drawn attention to the difference in response to isolated haemorrhage and haemorrhage associated with tissue damage—due to the nociceptive reflexes associated with injury. To quote directly from Stoner, 'if the prime aim of the physiological responses of the ebb phase is to maintain adequate oxygen transport to the tissues, particularly in those organs on which life depends, then it must be admitted that in some cases they fail'.

In a series of retrospective and prospective studies in postoperative patients it has been shown that survival is increased if V_{O_2} is maintained at higher than normal levels by providing a supranormal CI and D_{O_2}[5,9]. Following the initial measurements of V_{O_2}, D_{O_2} and $S_{\bar{v}O_2}$ in our patients, all necessary therapy was provided—fluids, blood transfusion, inotropic support and adjustment of mechanical ventilation in order that D_{O_2} was equal to or above the known optimal level. Oxygen consumption was thus maintained at high levels with low levels of $S_{\bar{v}O_2}$, avoiding potential tissue hypoxia and producing a favourable outcome in a group of patients with a high risk of death predicted by combined trauma and injury severity scores.

The risk of death was high in the group of patients studied but survival was greater than might have been expected[19]. It is the delivery of oxygen to the tissues which determines the metabolic response to injury and the maintenance of this above critical levels that determines outcome.

References

1 Cuthbertson DP. Observations on the disturbance of metabolism produced by injury to the limbs. *Quart J Med* 1932; **1**: 233–46.
2. Cuthbertson DP Post-shock metabolic response. *Lancet* 1942; **i** 433–7.
3. Wilmore DW The wound as an organ In: Little RA, Frayn KN, eds. *The Scientific Basis for the Care of the Critically Ill.* Manchester: Manchester University Press, 1986: 45–59.
4. Odling-Smee GW. The metabolic response to injury. In. Odling-Smee GW, Crockard A, eds. *Trauma Care.* London: Academic Press, 1981: 33–52
5 Shoemaker WC Circulatory mechanisms of shock and their mediators. *Crit Care Med* 1987; **15**: 787–94.
6 Little RA. Heat production after injury. *Br Med Bull* 1985; **41**: 226–31.
7 Stoner HB. Interpretation of the metabolic effects of trauma and sepsis. *J Clin Pathol* 1987; **40**: 1108–17.
8. Forrester JS, Ganz W, Diamond G *et al.* Thermodilution cardiac output determination with a single flow directed catheter *Am Heart J* 1972; **83**: 306–11.
9. Buran JM. Oxygen consumption. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago: Year Book Medical Publishing Inc., 1987. 16–21
10. Bland RD, Shoemaker WC, Abraham E, Cobo JC. Hemodynamic and oxygen transport patterns in surviving and non surviving postoperative patients *Crit Care Med* 1985; **13**: 85–90.
11. Shoemaker WC. Relationship of oxygen transport patterns to the pathophysiology and therapy of shock states. *Intensive Care Med* 1987; **13**: 230–43
12 Snyder JV. Patterns of hemodynamic response. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago: Year Book Medical Publishing Inc., 1987: 46–66
13. Shibutani K, Komatsu T, Kubal K. Critical level of oxygen delivery in anesthetized man. *Crit Care Med* 1983; **11**: 640–3.
14 Cournand A, Riley RL, Bradley SE *et al.* Studies of the circulation in clinical shock *Surgery* 1943, **13**: 964–95.
15. Shoemaker WC, Appel P, Czer LSC *et al* Pathogenesis of respiratory failure (ARDS) after hemorrhage and trauma. *Crit Care Med* 1980; **8**: 504–12.
16. Mixed venous oxygen saturation. Its role in the assessment of the critically ill patient. *Arch Int Med* 1983; **143**: 1400–2.
17 Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock. a study in man. *Anesthesiology* 1972; **36**: 472–8.
18 Kasnitz P, Druger GL, Yorra F *et al.* Mixed venous oxygen tension and hyperlactemia. Survival in severe cardiopulmonary disease. *JAMA* 1976; **236**: 570–4.
19 Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma* 1987; **27**. 370–8.

Paper accepted 10 February 1988

Br. J. Surg. 1988, Vol. 75, July,
693–696

Enterostomy as an adjunct to treatment of intra-abdominal sepsis

W. L. E. M. Hesp, E. J. C. Lubbers*, H. H. M. de Boer* and T. Hendriks*

*Department of General Surgery, Canisius/Wilhelmina Hospital, and *Department of General Surgery, St. Radboud University Hospital, Nijmegen, The Netherlands*

Correspondence to:
Dr W. L. E. M. Hesp, Department of General Surgery, Canisius/Wilhelmina Hospital,
P.O. Box 9015, 6500 GR
Nijmegen, The Netherlands

In 60 patients a small bowel enterostomy was constructed as part of the treatment of various intra-abdominal infectious and obstructive conditions. Eleven patients (18 per cent) died in the immediate postoperative period from continuing sepsis. In one patient closure of the stoma was not considered because of disseminated malignancy. In the remaining 48 patients continuity of the gut was subsequently restored. In 22 patients (46 per cent) complications occurred, 12 (25 per cent) of which were intra-abdominal septic complications. The occurrence of intra-abdominal complications was found to be linked to premature (i.e. within 3 months) closure of the stoma. Reasons for premature closure were stomal difficulties and prerenal azotaemia. Stomal closure was attended by a 10 per cent mortality rate.

Keywords: Small bowel, anastomosis, stoma, intra-abdominal sepsis

Establishing a colostomy to avoid the need for anastomosis or to protect a more distally located anastomosis is accepted practice in surgery of the colon in high risk situations. Several adverse circumstances, e.g. generalized peritonitis, intra-abdominal abscess and impaired circulation, are held responsible for an increased leakage rate in colonic surgery. We have demonstrated that under these conditions there is also an increase in the number of anastomotic failures in the small bowel and that the mortality from this complication is high[1]. A logical extension of experience gained in colonic surgery would be to apply the principle of enterostomy to special problems in small bowel surgery. There have been occasional advocates of the use of enterostomy in Crohn's disease[2,3] and in necrotizing enteritis in children[4]. Preliminary experience with its use in generalized peritonitis has been described by Mulholland and Delaney[5] and by ourselves[6]. It is our current policy to use an enterostomy after small bowel resection in the presence of peritonitis or intra-abdominal abscesses.

As far as we know, there exist no data in the literature concerning morbidity and mortality concomitant to the use of enterostomy in small bowel surgery. Therefore, we present our experience with 60 patients.

Patients and methods

In the period 1977–84 a small bowel split-enterostomy was established in 60 patients over the age of 16 years. There were 32 male patients and 28 female patients. Ages ranged from 19 to 76 years with a mean age of 45·7 (*Figure 1*). The mesentery of the bowel was divided as far as possible so as to bring the afferent limb out through a separate incision away from the main abdominal wound. A Brooke type ileostomy was always aimed at. The efferent limb was brought out either through the main wound or a separate wound, or oversewn and fixed to the parietal peritoneum to facilitate later retrieval. Patients were divided into four groups (*Table 1*) according to the presumed risk of the underlying disorder: group 1, postoperative peritonitis from abscess or anastomotic dehiscence; group 2, secondary peritonitis (appendicitis and perforated gastric/duodenal ulcer excluded), group 3, obstruction or fistula, and group 4, miscellaneous.

Group 1

Of the 31 patients with postoperative peritonitis 22 were referred to us by other institutions. In 17 of the subgroup of 19 patients with anastomotic dehiscence, treatment was by dismantling the anastomosis. The other two cases concerned leakages of sigmoid anastomoses which necessitated a Hartmann procedure plus a bowel resection (once because there was a strangulation obstruction of the intestine and once for an ischaemic right colon) with subsequent construction of a split-ileostomy. In the other subgroup of 12 patients, who underwent 1 or more laparotomies because of intra-abdominal abscesses, indications for performing an enterostomy were: iatrogenic small bowel lesions ($n=6$), enteritis of the distal ileum ($n=2$), small bowel perforation ($n=2$) and small bowel fistulae ($n=1$). A final patient with a jejuno-feeding fistula, because of a haemorrhagic necrotizing pancreatitis, developed intra-abdominal leakage, necessitating construction of a split-jejunostomy

Group 2

It has been our policy to avoid the construction of an anastomosis after resection of a small bowel segment in the presence of peritonitis. Seven patients with Crohn's disease received a split stoma because of free perforation ($n=2$), multiple fistulae with abscesses ($n=3$), or the presence of intraperitoneal masses with small accumulations of pus ($n=2$) In two patients with internal incarcerated hernia, necrotic small bowel had to be resected. Blunt abdominal trauma ($n=2$), in one patient coupled with a severe pancreatitis, had caused laceration of the distal ileum which had been in existence for 48 h at the time of the operation. The remaining five patients received a split-enterostomy for various reasons. free perforation in ulcerative colitis, multiple small bowel perforations in gallstone ileus, a foul-smelling necrotic bowel segment in mesenteric infarction, a perforated metastasis in carcinomatosis peritonei and a sigmoid perforation with fibrinous adhesions between small intestine and sigmoid colon.

Group 3

Indications for enterostomy in the patients from group 3 were: the presence of repeated enterocutaneous fistulae ($n=2$), rectovaginal fistula in ulcerative colitis ($n=1$), massive intestinal distension ($n=2$) and fistulae at multiple levels ($n=4$).

Group 4

Two of this miscellaneous group suffered from gastrointestinal blood loss with Crohn's disease or irradiation enteritis, and a temporary split-enterostomy was performed in order to ascertain if sufficient tissue had been resected The third patient developed necrotizing enteritis of the entire colon and distal ileum after a burn injury Finally, a patient with extensive malignant infiltration in the left abdomen, associated with a sigmoid carcinoma and diverticulitis, received a temporary split-ileostomy.

The enterostomies were distributed throughout the small bowel. 14 in the jejunum, 16 in mid-ileum and 30 in the terminal ileum.

Altogether 243 laparotomies were performed on these 60 patients Bowel preparation was not practised and antibiotic cover was not routinely given for these small bowel operations Anastomoses were of the two-layer kind of Vicryl 3-0 (Ethicon Ltd, UK). In analysing the

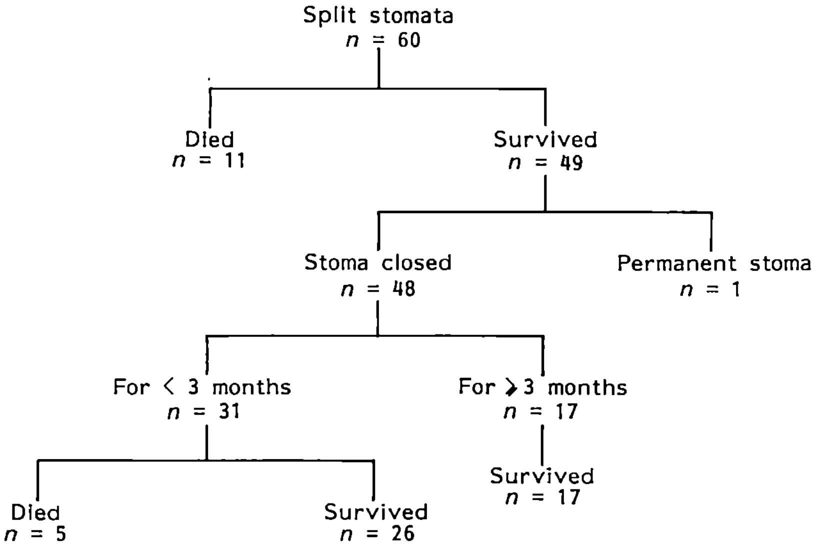


Figure 1 *Results of treatment in 60 patients with split stomata*

Table 1 *Indications for establishing an enterostomy on the small bowel*

Group 1. postoperative peritonitis	31
Anastomotic dehiscence	19
Underlying disorder	
Sigmoid carcinoma	2
Mesenteric infarction	3
Bifurcation prothesis	1
Crohn's disease	4
Incarcerated hernia	2
Irradiation enteritis	1
Multiple fistulae	1
Bricker loop	3
Haemophilia	1
Myxoma peritonei	1
Intra-abdominal abscesses	12
Underlying disorder	
Gastric resection	2
Incarcerated hernia	1
Appendicectomy	5
Blunt abdominal trauma	1
Pancreatitis	1
Cholecystectomy	1
Retroperitoneal lymphadenectomy	1
Group 2: secondary peritonitis	16
Underlying disorder	
Blunt abdominal trauma	2
Sigmoid perforation	1
Crohn's disease	7
Incarcerated hernia	2
Ulcerative colitis	1
Perforated gallstone ileus	1
Mesenteric infarction	1
Perforated metastasis	1
Group 3. obstruction/fistulae	9
Underlying disorder	
Postoperative fistula	2
Volvulus	1
Crohn's disease	4
Iatrogenic lesion after laparoscopy	1
Rectovaginal fistula	1
Group 4: miscellaneous	4
Underlying disorder	
GI haemorrhage in·	
Crohn's disease	1
Irradiation enteritis	1
Necrotizing enteritis	1
Ingrown sigmoid carcinoma	1

outcome of these procedures complications were tabulated and correlations were sought with the following factors serum albumin, renal function (urea, creatinine), liver function (bilirubin, alkaline phosphatase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase) and the time which elapsed between construction of the stoma and re-establishment of continuity of the gut.

Results

Eleven patients died, between 2 and 85 days (mean 32 days) after establishment of the enterostomy, from irreversible intra-abdominal sepsis and multiple organ failure (*Figure 1*). The mean age of these patients was 56 years (range 21–73 years). Nine patients belonged to group 1 and two to group 2. In one patient the continuity was not restored because of the presence of disseminated malignancy.

Of the 48 survivors whose stomas were subsequently closed, 21 could leave the hospital for further recovery at home. Two of these had to be re-admitted earlier than foreseen because of dehydration, while the remaining 19 were electively re-admitted for closure of the stoma In all, 29 patients needed in-hospital intravenous feeding because of the necessity of fluid and electrolyte replacement. Daily loss from the stoma measured >1 litre in six patients, >1·5 litres in seven patients, >2 litres in eight patients and >3 litres in two patients. For the remaining six patients the exact amount could not be calculated from the notes. All patients received parenteral nutrition through a subclavian infusion. In 21 patients this had to be continued until closure of the stoma.

In these 48 patients 62 bowel anastomoses were constructed (*Table 2*). Some patients received more than one anastomosis because they had more than one stoma or because of iatrogenic lesions during the operation as a consequence of dense

Table 2 *Number and localization of anastomoses*

Anastomosis	*n*
Jejunojejunostomy	11
Jejuno-ileostomy	1
Jejunocolostomy	1
Ileo-ileostomy	31
Ileocolostomy	14
Colocolostomy	4

Table 3 *Complications of stomal closure in 22 patients*

Complication	*n*
Wound infection	6
Pneumonia	1
Pulmonary embolism	1
Dehiscence abdominal wound	2
Intra-abdominal abscess	2
Bladder fistula	1
Enterocutaneous fistula	2
Dehiscence anastomosis	7

Continuity of the small bowel was restored in 48 patients: the main wound was closed 20 times and left open in 28 cases; numbers for the stomal wound were 6 and 42, respectively

adhesions. Complications after closure of the enterostomy occurred in 22 patients (46 per cent, *Table 3*). Wound complications were seen exclusively in those patients where the skin and subcutaneous tissues of the wound had been closed. Intra-abdominal complications were seen in 12 patients (25 per cent) after closure of the enterostomy. It is to be noted that in two patients an intra-abdominal abscess occurred which was caused by a bowel perforation at some distance from the intact anastomosis. Intra-abdominal complications occurred exclusively in patients where the stoma was closed within 3 months (*Table 4*). The time lapse between stomal construction and closure was significantly less ($P = 0{\cdot}005$, Wilcoxon test for two random samples) in patients with subsequent intra-abdominal complications than in patients where no complications occurred. More generally, this time interval was also significantly ($P = 0{\cdot}017$) smaller in patients with complications than in patients without complications. Disturbances in renal function and in liver function showed no statistically significant relation with the emergence of complications. A serum albumin level of <35 g/l was present in 47 per cent of patients with intra-abdominal complications against 9 per cent of patients without these complications ($P = 0{\cdot}01$, Fisher's two-sided exact test for a 2 × 2 table).

The further course of the patients with intra-abdominal complications is given in *Table 5*. The mean age of the five patients who died was 63·5 years which was significantly ($P = 0{\cdot}008$, Wilcoxon) higher than the mean age of the patient who survived. The mortality rate associated with closure of the enterostomy was 10 per cent and occurred exclusively in patients belonging to group 1. Total mortality in group 1 was 14 out of 31 patients (45 per cent), in group 2 it was 2 out of 16 patients (12 per cent) and in groups 3 and 4 nil. Due to the relatively small numbers this obvious trend could not be shown to be statistically significant.

Discussion

Establishment of an ileostomy or a jejunostomy as part of the treatment for the conditions affecting this series of patients is sound in theory. Suturing the bowel under septic conditions carries a high risk, as again demonstrated by the fact that in this series oversewing of small leaks was followed by renewed leakage in more than 50 per cent of iatrogenic lesions and in 100 per cent of anastomotic leaks. However, establishing an enterostomy in this type of patient has obvious drawbacks: loss of fluid and electrolytes, loss of resorptive surface and the necessity of a further operation to re-establish continuity of the gut.

Closure of the enterostomy was accompanied by a complication rate of 46 per cent. The complications can be divided into intra-abdominal complications and 'other' complications. Among the other complications wound infection was the most common and was seen when the wound was closed completely. Wound infection did not occur when the skin was left open, whilst hospital stay was not prolonged by this practice. Thus, the occurrence of wound infection in these patients may be largely preventable. Intra-abdominal complications were found to be significantly correlated with the time interval between construction and closure of the stoma and with the serum albumin level. Both are obviously related to the clinical course and condition of the patients. Those patients (19) who could be sent home and re-admitted electively constitute a favourable group with no continuing infection, with easily correctable fluid loss, normal oral intake and thus a normal albumin level. No intra-abdominal complications after closure of the stoma were seen in this group The two major reasons for premature (i.e within 3 months) closure of the enterostomy in the in-hospital group were stomal difficulties and prerenal azotaemia. The stoma had often to be established under suboptimal conditions: emergency operation; mesentery infiltrated, thickened and shortened by intraperitoneal infection; loops of bowel glued together by dense adhesions, site of stoma in the bowel dictated by the site of the leak; choice

Table 4 *Time interval between construction and closure of stoma related to the occurrence of complications*

Time interval	Number of patients without complications	Number of patients with complications	Total
2–4 weeks	3	5 (4)	8
4–8 weeks	6	7 (3)	13
8–12 weeks	3	7 (5)	10
>3 months	6	2	8
>4 months	4		4
>6 months	3		3
>9 months	1	1	2
Total	26	22	48

The number of patients with intra-abdominal complications is shown in parentheses

Table 5 *Intra-abdominal complications after closure of split-stomata treatment and results*

Patient	Age	Sex	Treatment and complications	Results
Fistula and abscess				
1	21	M	D + O	AW
2	49	M	D + R/A	AW
Enterocutaneous fistula				
3	44	F	Cons + R/A	AW
4	31	F	Cons + R/A	AW
5	64	F	Cons	†
Anastomotic dehiscence				
6	21	M	O L SS A L SS A	AW
7	25	F	SS A	AW
8	50	F	R/A	AW
9	68	M	SS	†
10	64	F	O	†
11	68	M	SS	†
12	60	F	O L SS R/A L R/A L R/A L SS	†

D, drainage; O, oversewn, R, resection; A, anastomosis, Cons, conservative, SS, split-stoma; L, leakage, AW, alive and well; † died of position of stoma in the abdominal wall limited by scars from previous incisions and drains.

All this may result in technically deficient stomas posing problems in care which even an experienced stomal therapist cannot overcome. Our practice has been to restore continuity in these cases early, but in the light of the experience presented here we think that an attempt at refashioning of the stoma might be wiser. In 14 patients the stoma had to be closed within 3 months because of prerenal azotaemia. The same problem has been met in children with necrotizing enterocolitis[7]. The loss of fluid and electrolytes in these patients with a high output fistula has to be compensated by long-term parenteral nutrition with its attendant complications[11]. In our series, 21 out of 48 patients needed prolonged parenteral nutrition, on average 8·5 ± 3·9 (s.d.) weeks, until closure of the stoma. Where possible, use of the enteral route is to be preferred. Mulholland and Delaney[5] reported good results from the use of a proximal diverting enterostomy. The drawback of this technique is the intra-abdominal presence of possibly dangerous suture lines This drawback does not exist in our technique, where a split stoma is constructed either through the offending lesion (e g. after dismantling a leaking anastomosis) or after its resection. Also, the distal bowel may be safely used for the return of the losses from the proximal bowel. So far, our experience in this respect is limited However, by doing this, it may be possible to avoid premature closing of the stoma.

Restoration of the continuity had a higher mortality in the small bowel than in the colon. Reconstruction of a colostomy carries a mortality rate of approximately 2 per cent[8–10]. After closure of the small bowel stoma we found a mortality rate of 10 per cent in adults, which is the same as that reported by Cogbill and Millikan[7] in children. The cause of death of the five patients, all belonging to the postoperative peritonitis group (1), was anastomotic dehiscence after the stoma had been closed within 3 months.

Under normal circumstances, our policy is to refrain from bowel preparation in patients undergoing small bowel resection, since morbidity (e.g. anastomotic dehiscence) is minimal[1]. However, it might be argued that in the current group of patients, whose general condition is moderate to poor and where bacterial overgrowth may exist in closed loops, bowel preparation and antibiotic cover would have been expedient.

Morbidity and mortality being considerable, the indication for enterostomy of the small bowel needs to be restricted to patients with postoperative intra-abdominal sepsis or generalized peritonitis, who need an intestinal resection. In cases of more localized disorders (e.g. groups 3 and 4) one should aim for construction of an anastomosis in healthy tissue. We have found indications that jejunal anastomoses are more resistant to infected conditions than anastomoses in the distal ileum[1]. Therefore, in cases of jejunal resection, a primary anastomosis could possibly be considered.

Prognosis of patients with postoperative intra-abdominal sepsis or with primary peritonitis, not originating in duodenal ulcer or appendix, is poor with a mortality rate of between 50 and 60 per cent[12,13]. Aggressive treatment with reoperations when required and elimination of the cause of the infection has ameliorated the outlook[14]. Avoiding anastomoses by establishing enterostomies is one way to achieve this. Continuity is restored only when the septic process has been brought under control.

This second operation had a mortality rate of 10 per cent, which brings the total mortality rate for groups 1 and 2 to 34 per cent which compares well with literature data. This retrospective study suggests that possible ways to lower mortality further might be: optimal construction and, if necessary, reconstruction of the stoma; where possible, enteral return of stomal effluent; and patience, preferably for 3 months or longer.

References

1 Hesp WLEM, Lubbers EJC, de Boer HHM, Hendriks T. Anastomotic insufficiency in small bowel surgery—incidence and treatment. *Langenbecks Arch Chir* 1986; **368**: 105–11.

2 Menguy R Surgical management of free perforation of the small bowel complicating regional enteritis. *Ann Surg* 1972; **175**: 178–89.

3. Goligher JC Resection with exteriorization in the management of faecal fistula originating in the small intestine. *Br J Surg* 1971, **58**. 163–7

4. Touloukian RJ. Neonatal necrotizing enterocolitis: an update on etiology, diagnosis and treatment. *Surg Clin North Am* 1976, **56**: 281–98

5 Mulholland MW, Delaney JP Proximal diverting jejunostomy for compromised small bowel *Surgery* 1983; **93**: 443–7.

6. Lubbers EJC, van der Sluis RF, de Boer HHM, Gimbrère JSF. Split enterostomy in the treatment and prevention of small bowel leakage. In: de Boer HHM, ed *Intra-abdominal Sepsis* Utrecht. Bunge, 1979. 104–9.

7. Cogbill TH, Millikan JS. Reconstitution of intestinal continuity after resection for neonatal necrotizing enterocolitis. *Surg Gynecol Obstet* 1985; **160**. 330–4.

8 Rosen L, Friedman IH Morbidity and mortality following intraperitoneal closure of transverse loop colostomy. *Dis Colon Rectum* 1980, **23**· 508–12.

9. Varnell J, Pemberton LB. Risk factors in colostomy closure. *Surgery* 1981; **89**: 683–6.

10. Freund H, Raniel J, Muggia-Sulam M. Factors affecting the morbidity of colostomy closure. *Dis Colon Rectum* 1981; **25**: 712–15

11. Rothstein FC, Halpin TC Jr, Kliegman RJ *et al* Importance of early ileostomy closure to prevent chronic salt and water losses after necrotizing enterocolitis *Pediatrics* 1982, **70**· 249–53.

12 Bohnen J, Boulanger M, Jonathan RN, Meakins L. Prognosis in generalized peritonitis. *Arch Surg* 1983; **118**· 285–90

13 Stephen M, Loewenthal J Generalized infective peritonitis *Surg Gynecol Obstet* 1978, **147**: 231–4.

14. Hudspeth AS. Radical surgical debridement in the treatment of advanced generalized bacterial peritonitis. *Arch Surg* 1975; **110**: 1233–1236

Paper accepted 31 January 1988

Br. J. Surg. 1988, Vol. 75, July,
697–699

Screening for breast cancer: some clinical aspects

A. D. Stockdale, P. Last*, A. K. Tucker† and J. Meirion Thomas‡

*Departments of Radiotherapy and ‡Surgery, Westminster Hospital, London, *Women's Unit, BUPA Medical Centre, London, and †Department of Radiology, St Bartholomew's Hospital, London, UK*

Correspondence to:
Mr J. Meirion Thomas,
Westminster Hospital, Dean Ryle Street, London SW1P 2AP, UK

There is little doubt that screening by palpation and mammography will reduce the mortality from breast cancer. Most of the studies have been designed to test survival difference and, following diagnosis, patients were treated by a variety of surgeons and methods. We present clinical and pathological data on 32 asymptomatic patients who were screened and found to have breast cancer. Investigation and treatment was performed by one surgeon according to a defined protocol. We confirm that mammography is a more sensitive diagnostic tool than palpation and describe how a review of the patient with the suspicious mammogram will increase the incidence of palpable tumours. We stress the importance of fine-needle aspiration cytology as a diagnostic and localization method. The low incidence of axillary node metastasis in patients with invasive carcinoma is described. More importantly, no patient in this series required treatment by mastectomy. In our experience patients with breast cancer detected by screening are eminently suitable for treatment by breast conservation.

Keywords: Breast carcinoma, screening, treatment, prognosis, cytology, axillary dissection

The first evidence that screening could reduce the mortality from breast cancer was provided by the HIP study[1] (Health Insurance Plan, New York) and it is important to note that in this study, the majority of tumours were detected by palpation rather than mammography. In all subsequent studies mammography has been shown to be a better diagnostic method than palpation, reflecting improvements in mammographic techniques and resolution. The optimistic results of the HIP study have been confirmed by two Dutch case-control studies[2,3] and by a randomized study from Sweden[4] which reported a 30 per cent reduction in mortality among screened patients as well as a 25 per cent reduction in stage II disease. These studies imply that it is possible, at least in some cases, to diagnose and treat breast cancer before it disseminates.

A surgeon seeing patients referred from a screening programme faces a number of problems not often experienced in the normal breast clinic. Many of the patients will have impalpable abnormalities and a surgeon must decide, in collaboration with the radiologist, which patients should be investigated by a localization procedure and biopsy and which patients can be deferred for review by clinical examination and repeat mammography. Furthermore the surgeon will need to be familiar with the literature on the treatment of ductal carcinoma *in situ* and lobular carcinoma *in situ*, and have formulated a treatment plan for such patients.

Our investigation was designed to obtain clinical and pathological data on patients found to have breast cancer by screening, to investigate the place of fine-needle aspiration cytology (FNAC) in a screening programme and to test the suitability of such patients for treatment by breast conservation and radical radiotherapy.

Patients and methods

Patients in this study were self-referred with the approval of their general practitioner to the BUPA Medical Centre, London. Those patients with any breast symptom at the time of first attendance were excluded from the study. Part of the total screening programme offered to patients is screening for breast cancer. Each woman is interviewed by a specially trained nursing sister who takes a detailed past and present history of any breast problem as well as a family history. The sister teaches breast self-examination individually, and carries out a clinical examination, carefully recording her findings. Two-view mammography (craniocaudal and oblique) is then performed on all new patients aged 35 and over. Unless symptoms develop, patients are advised not to have further mammography until 40 years of age, from which time annual oblique-view mammography is recommended. Mammography is undertaken in women under 35 years where there is a palpable breast mass or a family history of breast cancer in young first-degree relatives. Patients with any abnormality on breast palpation or mammography are referred back to their general practitioner for advice and further investigation. At the same time the practitioner is offered the services of the surgeon attending the Medical Centre Special Breast Clinic. This paper describes the experience of one surgeon using the following treatment policy.

In patients with palpable abnormalities, FNAC was performed and, providing a good cellular smear was obtained, patients were managed according to the results. Those with benign smears were reassured, reviewed by palpation and FNAC at 3 months and then returned to annual screening. To date we know of no patient in this group in whom the cytology was false-negative. Patients with mammographic changes reported as suspicious or highly suspicious of malignancy were investigated by FNAC and biopsy preceded by a localization procedure when necessary. Patients with equivocal mammographic changes had mammograms repeated at 6 and 12 months and if there was no change they were returned to annual screening.

Two localization techniques were used for totally impalpable mammographic abnormalities. For lesions that were superficial or peripheral in the breast, mammogram-directed FNAC was performed. Patients with negative cytology and those with deep, central lesions underwent localization by a wire technique similar to that described by Frank *et al.*[5]. Palpable and localized tumours were widely excised with a margin of 1 cm of macroscopically normal breast tissue. With the exception of the two patients with small medial tumours, all patients with invasive carcinoma were treated by ipsilateral radical axillary dissection (RAD) to the outer border of the first rib through a separate axillary incision. All 32 patients, including those with ductal carcinoma *in situ*, were treated by radical radiotherapy by a standard technique[6] but in those patients in whom a RAD had been performed the axilla was specifically excluded from the field of the irradiation.

Results

In 32 patients, 37 cancers were detected. Five patients had two cancers each in the same breast (*Table 1*). The mean age was 52 (range 37–72) years. With regard to site, 18 tumours were lateral, 12 central and 7 medial. Three patients had previously been treated for breast cancer: two developed a contralateral primary tumour and the third patient developed a second primary in the same breast away from the initial site, having

Table 1 *Histology in five patients, each with two carcinomas in the same breast, no patient with two carcinomas had mixed histology*

	No of patients
Two invasive duct carcinomas	3
Two foci of ductal carcinoma *in situ*	1
Two foci of lobular carcinoma *in situ* with minimal invasion	1
Total	5

Table 2 *Histology of 37 breast cancers in 32 patients*

	No. of cancers
Ductal carcinoma *in situ*	5
Ductal carcinoma *in situ* with minimal invasion	6
Invasive ductal carcinoma	24
Lobular carcinoma *in situ* with minimal invasion	1
Invasive lobular carcinoma	1
Total	37

been treated 5 years previously in France by hemimastectomy and adjuvant chemotherapy.

The histological type of tumour is given in *Table 2*. The tumour grade of the invasive duct carcinomas was carefully reviewed according to the method described by Elston *et al.*[7]. The distribution of tumour grade (I–III) was similar to that expected in a group of patients with symptomatic breast tumours and there was no suggestion that smaller tumours detected by screening were better differentiated than those seen in symptomatic women. Of the 32 patients, 15 had been screened previously. The major pathological prognostic factors in the 15 incident cancers and 17 prevalent cancers were compared and no difference was found in the two groups with regard to carcinoma *in situ*, primary tumour size, tumour grade or node positivity. These major pathological prognostic factors fall equally into both groups.

The mean maximum tumour diameter of the 25 invasive cancers (in 22 patients) was 13·8 mm (range 6–35 mm). Of these 22 patients, RAD was performed in 20 and 4 had axillary node metastases (2 of 9, 1 of 13; 4 of 14 and 7 of 11 nodes positive). Two patients with small medial tumours did not have RAD.

Of the 32 patients with breast cancer, a mass was palpated by the screening sister in 9, confirmed by the surgeon and FNAC was positive in 8. In 11 patients in whom a mass was not detected by the screening sister, a mass was palpated by the surgeon with the aid of the suspicious mammogram and FNAC was positive in 10 patients, while 1 patient underwent wire localization. In the remaining 12 patients, no tumour was palpable but in 5 of these mammogram-directed FNAC was positive and 7 wire localizations were required.

In 29 of the 32 patients with cancer, the mammogram was reported as suspicious or highly suspicious of malignancy. In the remaining three patients, abnormalities were noted on the mammogram and reported as radiologically benign, but in all three patients the lesion was palpable and positive FNAC was obtained Mammograms reported as normal had previously been performed in 15 of 32 patients and the median interval between the normal and the suspicious mammogram was 18 (range 12–49) months. On review none of these mammograms have been considered to be false-negative but one patient who was advised to have repeat X-ray at 3 months did not reappear for 1 year.

A further 16 patients with a suspicious mammogram but impalpable disease had wire localization performed and were proven to have benign breast disease.

All patients remain well and disease-free at a median follow-up interval of 26 (range 13–43) months.

Discussion

There is increasing evidence that screening for breast cancer reduces mortality from the disease but there has been little discussion in the literature of the management of these early cases.

The acceptability of treatment will undoubtedly affect the willingness of patients to enter a screening programme. In the screening programmes published only 65–90 per cent of women offered screening accepted the invitation[1–4,8] and this surprisingly low compliance rate may be partly explained by the fear of mastectomy and its associated morbidity if cancer were detected. In this study of screened, asymptomatic patients with breast cancer, all were suitable for treatment by breast conservation.

Inevitably the benefit of any screening programme must be balanced against the cost and it is important to minimize the number of biopsies for benign disease. In this study, this was achieved by using strict mammographic criteria of radiological suspicion and by the use of FNAC positively to exclude palpable benign disease. In this way, excision biopsy was performed in 48 patients, 32 (67 per cent) of whom were proven to have breast cancer, giving a malignant:benign biopsy ratio of 1:0·5. In a series[9] where excision biopsy alone was used, only 20–30 per cent of lesions biopsied were malignant but indications for biopsy may occasionally be swayed by legal rather than medical criteria[10].

Mammography has been shown again to be more sensitive than palpation in detecting early breast cancer. However, when the breast is palpated with the knowledge of the precise site of a suspicious radiological abnormality, the incidence of palpable tumours was greatly enhanced and other authors have described similar experiences[8].

The importance of FNAC in the management of breast disease is well established[11]. The role of FNAC in breast cancer screening has previously been described[12] and we would like to stress its value. As well as contributing to the differentiation of benign from malignant palpable disease, mammogram-directed FNAC has been shown to have a role in the localization of impalpable disease.

Management of lobular carcinoma *in situ* and ductal carcinoma *in situ* of the breast remains controversial. There is, however, broad agreement that following biopsy alone there is an increased risk of invasive carcinoma of the same breast[13–15]. It is also recognized that these lesions may be both multicentric and bilateral and this has led some authors to recommend bilateral mastectomy as the treatment of choice[16]. Patients with invasive ductal carcinoma associated with ductal carcinoma *in situ* may be at an increased risk of local recurrence[17]. Nevertheless some studies have shown excellent local control for pure ductal carcinoma *in situ* treated by wide local excision and postoperative radiotherapy[18,19]. This policy was adopted in the present study. Where one or two foci of ductal carcinoma *in situ* were identified each was widely excised and followed by radiotherapy. In one patient where ductal carcinoma *in situ* was found to be present throughout the breast, a subcutaneous mastectomy was performed with delayed implant reconstruction 4 months after radiotherapy.

The low incidence of axillary node metastasis in patients with invasive carcinoma detected while asymptomatic is encouraging and confirms other reports[20–22]. The impact of positive axillary nodes on the prognosis of patients with breast cancer is well known, recent figures[23] showing an 87 per cent 5-year survival for patients with axillary node negative breast cancer but only 40 per cent 5-year survival if the lymph nodes contained metastatic disease.

The comparative pathology of prevalent and incident cancers detected by breast screening has been studied by Anderson *et al.*[24] reporting the Edinburgh Breast Screening Project They found that the detection of good prognosis tumours is favoured at the prevalence screens and faster growing, aggressive tumours are found at the subsequent incidence screens. The number of patients in our series is much smaller but the major pathological prognostic factors were compared and no difference was found between the prevalent and incident groups.

At present, the evidence is that breast screening will reduce mortality from breast cancer. Another great benefit of screening is that primary tumours can be detected when they are small, often impalpable and eminently suitable for treatment by breast conservation and radical radiotherapy. Therefore, as well as improving survival more patients can be spared the psychiatric and social consequences of mastectomy.

Acknowledgements

We are grateful to Dr John Firth for review of the histology. This work was supported by the Ken Oliver Research Trust.

References

1. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *J Am Med Assoc* 1971; **215**. 1777–85.
2. Verbeek ALM. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project 1975–1981. *Lancet* 1984; **i**. 1222–4.
3. Collette HJA. Evaluation of screening for breast cancer in a non-randomised study (the DOM project), by means of a case control study. *Lancet* 1984; **i**: 1224–6.
4. Tabar L. Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985; **i**: 829–32.
5. Frank HA, Hall FM, Steer ML. Preoperative localization of nonpalpable breast lesions demonstrated by mammography. *N Engl J Med* 1976; **295**. 259–60.
6. Ashford RFU, Phillips RH, Coe MA, Pickering DGL, Baily B, Ellis H. Conservative excision and radiotherapy for early breast cancer—an acceptable alternative? *Clin Oncol* 1984; **10**. 45–58.
7. Elston CW, Gresham GA, Rao GS *et al.* The Cancer Research Campaign (King's/Cambridge) trial for early breast cancer: clinico-pathological aspects. *Br J Cancer* 1982; **45**: 655–68.
8. Price JL, Thomas BA. Results of screening by mammography and clinical examination. In: Blamey RW, ed. *Breast Cancer*. London: Update Publications Ltd 1984: 15–19.
9. Frankl G, Ackerman M. Xeromammography and 1200 breast cancers. *Radiol Clin N Am* 1983; **21**: 81–91.
10. Hall FM. Screening mammography: potential problems on the horizon. *N Engl J Med* 1986; **314**: 53–5.
11. Meirion-Thomas J, Fitzharris BM, Redding WH *et al.* Clinical examination, xero-mammography and fine-needle aspiration cytology in diagnosis of breast tumours. *Br Med J* 1978; **ii**. 1139–41.
12. Lamb J, Anderson TJ, Dixon MJ, Levack PA. Role of fine needle aspiration cytology in breast cancer screening. *J Clin Pathol* 1987; **40**: 705–9.
13. Page DL, Dupont WD, Rogers LW, Landenberger M. Intraduct carcinoma of the breast. *Cancer* 1982; **49**: 751–8.
14. Betsill WL, Rosen PP, Lieberman PH, Robbins GF. Intraduct carcinoma. *J Am Med Assoc* 1978; **239**: 1863–7.
15. Anderson JA. Lobular carcinoma *in situ* of the breast. *Cancer* 1977; **39**: 2597–602.
16. Sunshine JA, Moseley HS, Fletcher WS, Krippaehne WW. Breast carcinoma *in situ*. *Am J Surg* 1985; **150**: 44–9.
17. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer* 1984; **53**: 1049–57.
18. Zafrani B, Fourquet A, Vilcoq JR, Legal M, Calle R. Conservative management of intraduct breast cancer with tumorectomy and radiation therapy. *Cancer* 1986; **57**. 1299–301.
19. Recht A, Danoff BS, Solin LJ *et al.* Intraduct carcinoma of breast. Results of treatment with excisional biopsy and irradiation. *J Clin Oncol* 1985; **3**: 1339–43.
20. Hutchinson J, Tucker AK. Breast screening results from a healthy working population. *Clin Oncol* 1984; **10**: 123–8.
21. Patchefsky AS, Shaber GS, Schwartz GF *et al.* The pathology of breast cancer detected by mass population screening. *Cancer* 1977; **40**: 1659–70.
22. Hoehn JL, Hardacre JM, Swanson MK, Williams GH. Localisation of occult breast lesions. *Cancer* 1982; **49**. 1142–4.
23. American Cancer Society. Facts and figures. 1983.
24. Anderson TJ, Alexander F, Chetty U *et al.* Comparative pathology of prevalent and incident cancers detected by breast screening. *Lancet* 1986; **i**: 519–22.

Paper accepted 1 January 1988

Br. J. Surg. 1988, Vol. 75, July,
700–701

Microdochectomy for single-duct discharge from the nipple

A. P. Locker,
M. H. Galea, I. O. Ellis,
H. W. Holliday,
C. W. Elston and
R. W. Blamey

Nottingham City Hospital,
Nottingham, UK

Correspondence to:
Mr A. P. Locker, Professorial Unit
of Surgery, City Hospital, Hucknall
Road, Nottingham NG5 1PB, UK

Microdochectomy has been the accepted treatment for single-duct nipple discharge. Review of 97 consecutive patients undergoing microdochectomy between 1980 and 1987 revealed a total of eight patients with ductal carcinoma in situ. *All of these had pre-operative mammography, results of which were highly suspicious of malignancy in six patients. Tiny foci of ductal carcinoma* in situ *were found in the two patients with normal mammograms. We suggest an expectant policy in cases where the mammogram is normal, omitting routine microdochectomy.*

Keywords: Nipple discharge, microdochectomy, mammography

Generally, single-duct discharge is considered to be of more significance than multiduct nipple discharge and may be caused by duct ectasia, duct papilloma or cancer. The aim of our study was to audit the result of microdochectomy as the operative procedure for all cases of single-duct discharge.

Patients and methods

Between March 1980 and March 1987, 97 microdochectomies were performed for single-duct nipple discharge at the City Hospital, Nottingham, under the care of one consultant surgeon (R W B)

All patients had a bloody, serous or coloured discharge arising from one duct. Each patient gave a history of spontaneous discharge and, in addition, a single discharging duct was identified during clinical examination by gentle pressure around the nipple If a breast lump was discovered on clinical examination or an opacity on mammography this took precedence and was managed appropriately Until now all the patients with spontaneous single-duct nipple discharge and without a palpable lump have undergone microdochectomy. Ductography and nipple discharge cytology were not used in any patients

The technique of microdochectomy as practised in Nottingham is as follows. under general anaesthesia a lacrimal probe is inserted into the discharging duct. A radial incision is then made on to the relevant duct which is dissected and excised, together with a cone of underlying breast tissue. The specimen is sent for histological examination and the wound closed with fine sutures.

We reviewed the case notes of all 97 patients and noted the result of pre-operative mammography, if performed, together with the pathology of the excised duct. In addition a detailed histological review has been made in all 97 patients by one pathologist (I.O.E.)

Results

The median age of the 97 patients was 47·5 years (range 25–77 years). In 72 per cent of patients there was no past history of breast problems and in 77 patients (79 per cent) a pre-operative mammogram had been taken. Omission of pre-operative mammography was for no specific reason; age, certainly, was not a factor. The median age of the 20 patients with no pre-operative mammography was 48·5 years (range 25–72 years).

Forty-six patients (47 per cent) had a bloodstained discharge at presentation. This group had a median duration of symptoms of 4 weeks before presentation. For patients with non-bloodstained discharge the median duration of symptoms was 10 weeks. The range of symptom duration was 1 week to over 4 years.

The histological abnormalities in the 97 patients are seen in *Table 1*, together with the mean patient age in each group.

A previous retrospective study[1], in Nottingham, identified 73 patients having microdochectomy between 1975 and 1980. The results are seen in *Table 2* with the total numbers from both studies combined. In this earlier review two of four patients with ductal carcinoma *in situ* had pre-operative mammography. Both were positive.

The histological review of the microdochectomy specimens from the period 1980–87 allowed further breakdown of the benign breast conditions. The results are shown in *Table 3.*

In the most recent study, six patients had ductal carcinoma *in situ* only; two patients had ductal carcinoma *in situ* with microinvasion. All eight patients had pre-operative mammography. In six patients (including both with microinvasion) the mammograms gave rise to a high degree of suspicion of malignancy.

Histological examination of the excised ducts in the two patients with normal mammograms showed only tiny foci of ductal carcinoma *in situ*. Both these patients had presented with a bloodstained discharge. Three of the eight patients with ductal carcinoma *in situ* were under the age of 50 years; the youngest was 38 years old.

Of the 89 patients with benign conditions in whom mammography was performed, results in 10 were suggestive of carcinoma.

Discussion

The management of patients with single-duct nipple discharge and without a palpable breast lump remains controversial.

Some workers have attempted to correlate the type of discharge with the probable pathological cause[2,3]. In our study, as in others[4–7], it seems that an overtly bloodstained discharge

Table 1 *Pathology results this study* (n = *97*)

Pathological diagnosis	No of patients	Median age (years)	Percentage with bloodstained discharge
Ductal carcinoma *in situ*	8	51	62·5
Intraduct papilloma	46	48·5	48
Other benign breast lesions	42	46	45
Dense fibrous tissue No specific abnormality	1	—	—

Table 2 *Pathology results this study plus previous retrospective study*[1] (n = *170*)

Pathological diagnosis	Number of patients
Ductal carcinoma *in situ*	12
Intraduct papilloma	77
Other benign breast disease	80
No specific abnormality	1

Table 3 *Breakdown of benign conditions diagnosed at microdochectomy, 1980–87* (n = 89)

Pathological diagnosis	Number of patients
Papilloma	46
Solitary	41
Multiple	5 (2 associated with atypical ductal hyperplasia)
Duct ectasia	31
Fibrocystic disease	9
With atypical ductal hyperplasia	1
With epithelial hyperplasia	5
Without epithelial hyperplasia	3
Chronic suppurative inflammation	2
'Normal' (dense fibrous tissue, no specific abnormality)	1

does not necessarily herald a malignant lesion. We found that patients with benign ductal papilloma and duct ectasia presented with bloodstained discharge in 48 per cent and 45 per cent of cases respectively. Conversely, three out of eight patients with ductal carcinoma *in situ* presented with serous discharge. Chaudary and colleagues[8] have shown that ductal carcinoma *in situ* always presents with a haemoglobin-positive discharge even if the latter was serous to the naked eye. Ductal papilloma, however, also showed positive discharge in 107 out of 132 cases (81 per cent).

Recent work[9] supports the view that there are two types of papilloma: those arising in large ducts at the centre of the duct system and those arising in the small ducts at the periphery of the duct system. Papillomas arising in the central large ducts tend to be solitary and are regarded as having a low risk of malignancy[10]. Papillomas arising in the periphery of the duct system are frequently multiple and are more commonly associated with epithelial hyperplasia, ductal carcinoma *in situ* and invasive carcinoma[11]

All five of our cases with multiple papillomas had involvement of small extra- or intralobular ducts; three also had involvement of large segmental and subsegmental ducts. Of the five cases, four had coexistent epithelial hyperplasia, two fulfilling the criteria for atypical ductal hyperplasia[12]. The finding is consistent with the view that peripheral multiple papillomas are more likely to progress to malignancy.

The ratio of solitary to multiple papillomas in our study (8:1) is similar to that previously reported by Haagensen[13], who also points out that patients with multiple papillomas present with nipple discharge much less frequently than cases of solitary papillomas. Thus the more 'pre-malignant' lesions are less likely to present with nipple discharge.

Conventional mammography has been claimed to be of little value in the patients with single-duct discharge unless there is an associated mass[14,15], although contrast mammography (ductography) is considered to be more helpful[16,17]. In this review, however, we have shown that six out of eight patients with histologically proven ductal carcinoma *in situ* had preoperative mammograms suggestive of malignancy. The two patients with normal mammograms had tiny foci of ductal carcinoma *in situ* which should have become apparent on a follow-up mammography.

Ductal carcinoma *in situ* was not confined in this series to elderly patients, although the median age of this group is higher than that of benign conditions (*Table 1*). The youngest patient was diagnosed at 38 years of age and hence we would not suggest that age be considered in the decision whether to perform mammography.

We would therefore propose that, after clinical examination, patients with abnormal mammograms undergo microdochectomy and that the remainder are followed up by a repeat mammogram at 1 year and subsequently at yearly intervals only if their discharge persists. Patients with profuse and embarrassing discharge or those worried by their discharge, could have therapeutic microdochectomy at their choice.

In this retrospective study, had we followed such an expectant policy, only 16 patients in place of 97 would have needed microdochectomy.

References

1. Holliday H, Hinton C Nipple discharge and duct ectasia. In. Blamey RW, ed *Complications in the Management of Breast Disease* London: Bailliere Tindall, 1986· 26–32.
2. Fishermann K, Bech I, Foged P, Hostrup P, Lauritsen JB Nipple discharge: diagnosis and treatment *Acta Chir Scand* 1969, **135**. 403–6.
3. Leis HP, Pilnik S, Dursi J, Santoro E. Nipple discharge. *Int Surg* 1973; **58**. 162.
4. Rimsten A, Skoog V, Stenkvist B On the significance of nipple discharge in the diagnosis of breast disease. *Acta Chir Scand* 1976; **142**: 513–18.
5. Lewison EF, Chambers RG. Clinical significance of nipple discharge. *JAMA* 1951; **147**· 295–9.
6. Seltzer MH, Perloff LT, Kelly RI, Fitts WT The significance of age in patients with nipple discharge *Surg Gynecol Obstet* 1970, **131**: 519–22.
7. Haagensen CD. *Diseases of the Breast*, 2nd edn. Philadelphia: W.B. Saunders, 1971: 253–4.
8. Chaudary MA, Millis RR, Davies GC, Hayward JL. Nipple discharge. The diagnostic value of testing for occult blood. *Ann Surg* 1982; **196**. 651–5.
9. Ohuchi N, Aber R, Takahashi T, Tezuka F. Origin and extension of intraductal papillomas of the breast: a three-dimensional reconstruction study *Breast Cancer Res Treat* 1984; **4** 117–28
10. Carter D. Intraductal papillary tumours of the breast. *Cancer* 1977; **39**: 1689–92.
11. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of human breast with special reference to possible precancerous lesions. *J Natl Cancer Inst* 1975; **55**: 231–73
12. Page DL, Dupont WD, Rogers LW, Winfield AC. Atypical hyperplastic lesions of the female breast A long term follow-up study *Cancer* 1985; **55**: 2698–708.
13. Haagensen CD. *Diseases of the Breast*, 2nd edn. Philadelphia, W.B. Saunders, 1971: 277–8.
14. Editorial. Discharge from the nipple. *Lancet* 1983, **ii**. 1405.
15. Urban JA, Egeli RA. Non-lactational nipple discharge. *CA* 1978, **28**· 130–40.
16. Funderburk WW, Syphax B. Evaluation of nipple discharge in benign and malignant conditions. *Cancer* 1969; **24**. 1290–6.
17. Harris WG. Ductography for nipple discharge (letter). *Lancet* 1984; **i**: 110.

Paper accepted 17 January 1988

Br. J. Surg. 1988, Vol. 75, July,
702–704

Breast cyst type does not predict the natural history of cyst disease or breast cancer risk

S. R. Ebbs and T. Bates

The Breast Clinic, William Harvey Hospital, Ashford, Kent, UK

Correspondence to: Mr S. R. Ebbs,
Department of Surgery, Rayne
Institute, 123 Coldharbour Lane,
London SE5 9NU, UK

The sodium (Na) and potassium (K) concentrations were measured in the fluid of 169 breast cysts aspirated from 101 consecutive patients presenting to a single clinic. The Na/K ratio was used to define cysts as either apocrine (Na/K <3) or flattened (Na/K >3) in type. There was no consistency in the type of cyst for individual patients. Cyst type was not predictive of further cyst development, neither was a particular cyst type associated with the development of, or a history of, breast cancer.

Keywords: Benign breast disease, natural history, sodium/potassium ratio

Several reports and literature reviews have indicated that women with benign cystic disease of the breast may have an increased risk of breast cancer[1–3]. It has been suggested that breast cysts may be divided into two types according to the ratio of the concentrations of sodium (Na) and potassium (K) in the cyst fluid[4–6]: flattened cysts have a Na/K ratio of >3—these cation concentrations are similar to plasma; and apocrine cysts, which are lined by apocrine epithelium, have a ratio of <3—the fluid they contain is believed to accumulate by an active secretory process[6–8].

Previous studies have indicated that cyst type tends to remain constant for individual patients and that women presenting with apocrine cysts are more likely to develop further cysts[5,6].

Together with the observations that breast cancer risk becomes most pronounced in those who develop multiple cysts[3], that apocrine changes are more frequent in the populations at highest risk of breast cancer[5], and that histological risk factors for breast cancer may be more frequent in those with clinically palpable apocrine cysts[9], a hypothesis has arisen that patients with apocrine cysts are most likely to develop breast cancer[9]. We have sought to confirm these observations and to test this hypothesis.

Patients and methods

A prospective study was undertaken on all patients presenting for the first time with a palpable breast cyst to a single clinic over a period of 3·75 years Cations were estimated by flame photometry after appropriate dilution with lithium heparin solution

Following initial cyst aspiration patients were generally asked to return to the clinic twice at 6-weekly intervals The frequency and need for subsequent follow-up were determined by the clinical findings Patients were also asked to return if they noticed a new breast lump The clinical follow-up period ranged between 1 and 68 months with a mean of 12 months and a median of 5 months. At the time of analysis of the data it was at least 3 months since the last patient had been entered into the study.

Results

A total of 196 cysts were aspirated from 101 consecutive patients. Cations were measured on 169 (86 per cent); of the remainder 9 samples were too small, 1 sample was unsuitable for analysis and 17 samples were either not sent to or not received by the laboratory.

Cyst type

A bimodal distribution of cysts was found when typed by either Na, K or Na/K ratio; 93 cysts were classified as apocrine and 76 as flattened. An inverse relationship existed between Na and K concentrations ($r = 0{\cdot}96$, $P < 0{\cdot}001$).

Cyst type and risk of further cysts

The risk of further cyst development according to cyst type at presentation is shown in *Table 1.*

Cyst type and frequency

Figure 1 shows the ratio of apocrine to flattened cysts plotted against the total number of cysts aspirated from each patient, together with the same graph from the work of Dixon *et al.*[5]. In the current study it can be seen that there is only a slight increase in the relative frequency of apocrine cysts with total number of cysts, in contrast to the previous report.

Stability of cyst type

There were 15 patients who on 21 occasions had cation estimations performed on the fluid aspirated from multiple cysts at the same outpatient attendance. On 13 (62 per cent) of these occasions cysts were all of the same type. Twenty-two patients had cation estimations performed upon cysts aspirated at sequential outpatient visits. In eight (36 per cent) of these patients all cysts were of the same type.

Cyst type and cancer

Six patients had breast cancer diagnosed at or following aspiration of a cyst. Two patients had a previous history of breast cancer prior to cyst aspiration. Details of these eight patients are given in *Table 2.* Fisher's exact test revealed no significant difference in cyst type distribution when compared with the distribution in patients who did not develop breast cancer.

Table 1 *Cyst type at presentation and type of further cysts*

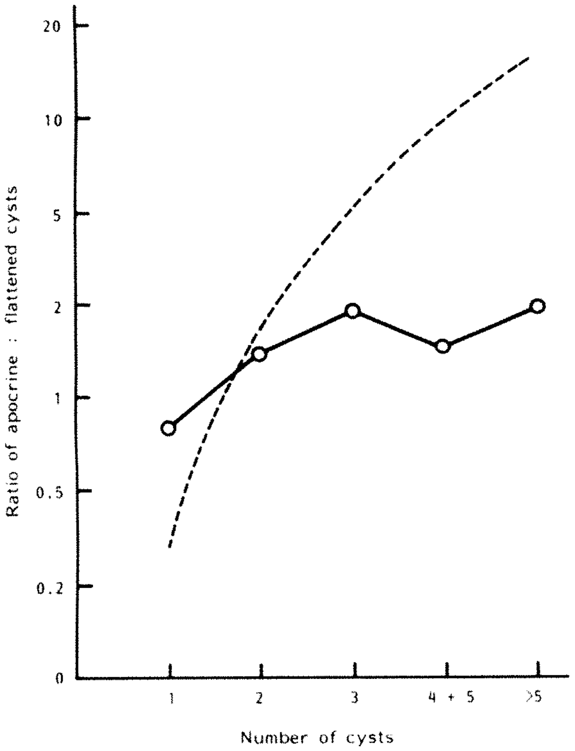
Cyst type at presentation	Further cysts No.	Further cysts Type
49 flattened	14	4 flattened 0 mixed 4 apocrine 6 not measured
3 mixed	2	1 apocrine 1 mixed
49 apocrine	16	3 flattened 5 mixed 7 apocrine 1 not measured

Numbers of patients shown
'Mixed' refers to multiple simultaneous cysts that were not exclusively of one cyst type

0007–1323/88/070702–03$3 00 © 1988 Butterworth & Co (Publishers) Ltd

Cyst type and age

No significant difference in the frequency of cyst type was found between patients who were under and those who were over 50 years of age. The age distribution for patients who underwent biopsy of benign breast disease was almost identical to that in patients who did not have a biopsy. The eight 'cancer' patients had a significantly higher age than 'non-cancer' patients (median ages 51 *versus* 43; $P<0{\cdot}05$).



	1	2	3	4 + 5	>5	Total
n	62	21	4	11	3	101
AC	29	19	7	21	17	93
FC	33	16	4	14	9	76
AC:FC	0·88	1·19	1·75	1·5	1·89	1·22

Figure 1 *The ratio of apocrine to flattened cysts in the groups of patients with 1, 2, 3, 4 and 5 and >5 cysts. The graph (---) is derived from the data of Dixon* et al.[5]. *The graph for the current study (○) is derived from the data shown. AC, apocrine cysts; FC, flattened cysts;* n, *number of patients*

Discussion

The extremely strong correlation demonstrated in this study confirms the inverse relationship between Na and K concentrations within breast cyst fluid. Cysts have a bimodal distribution tending to lie at extremes of the correlation line and so may be typed according to the ratio of Na/K. A division of 3 for this ratio has been suggested by Dixon *et al.* based on histological studies, and we have used this classification[5]. In this study 93 cysts could be typed as flattened and 76 cysts as apocrine.

Table 1 shows that for our patients the type of cyst aspirated at the first visit did not predict the likelihood of recurrence. *Figure 1* shows that the ratio of apocrine/flattened cysts did not change markedly with the number of cysts aspirated. This observation is not surprising when taken in conjunction with the findings that cyst type within an individual patient is not constant and does not remain stable with time. These findings are to be contrasted with the reports of Dixon *et al.* (shown in *Figure 1*) and Dogliotti *et al.* who have previously found consistency of cyst type for individuals and suggested that apocrine type is associated with multiple cysts and recurrent cyst development[4-6].

A heterogeneous group of patients are presented who either had a previous history of breast cancer (and so presumably 'abnormal' breast epithelium) or developed cancer of the breast which was diagnosed at the time of or after aspiration of a breast cyst. There was no suggestion of a special association between one cyst type and cancer. The women who developed both breast cancer and breast cysts were significantly older than those who did not have such an association.

Previous attempts to identify women who will go on to develop breast cancer, by cyst type, have encountered two problems. First, the control group may not be comparable with the high risk group[10]. Secondly, earlier studies have given inaccurate information regarding cyst formation and cancer risk. Recent large histological studies have indicated no great increase in the risk of breast cancer for women with cysts who do not have a family history of breast cancer[11].

This study indicates that the cation concentrations in breast cyst fluid may not remain constant for particular individuals. Consequently breast cyst type failed to predict the natural history of the cystic disease and cannot indicate the likelihood of the occurrence of cancer.

Although breast cysts may arbitrarily be divided into two types it seems likely that the Na and K concentrations do not predict the future behaviour of the epithelium. Breast cysts develop from microcysts which are all of an apocrine type, with

Table 2 *Cyst type and history of eight patients with an association of breast cyst and breast cancer development*

	Cyst at presentation		Further cysts		
Age	No.	Ratio Na/K	No.	Ratio Na/K	Cancer
Patients with a simultaneous or subsequent diagnosis of breast cancer:					
61	1	27·9	2	? 0·04	Stage III (part solid, part cystic) diagnosed 9 months after first cyst aspiration
74	1	27·3	1	?	Intracystic carcinoma diagnosed at first aspiration
47	1	17·3	0	—	Stage II cancer diagnosed 10 months after first aspiration
46	1	0·21	0	—	Lobular carcinoma *in situ* diagnosed at time of cyst aspiration
45	1	19·6	0	—	Stage III carcinoma contralateral breast diagnosed at time of aspiration
47	1	0·20	0	—	Stage II carcinoma adjacent to cyst
Patients with a previous history of breast cancer:					
56	1	26·8	0	—	Contralateral mastectomy 5 years previously
80	1	15·6	1	0·32	Cancer diagnosed 4 years previously. At time of aspirate had complete response to tamoxifen

high concentrations of K and sex steroids from active cellular secretion[12]. In at least a proportion it appears that the epithelium becomes flattened; active concentrating mechanisms may become less effective and rapidly the contents become more like that of plasma. This may simply represent an ageing change of a single type of cyst. Page and Dupont have noted that flattened cysts are larger than apocrine and suggest that flattened cysts represent the late stage of development in which the active element is no longer present[10]. This alternative hypothesis would explain our findings more readily than the current speculation that two types of abnormality result in different cyst types.

Acknowledgements

We wish to thank Mr R. P. A'Hern, Statistician at the Cancer Research Campaign, Clinical Trials Centre, for his help with the analyses, Dr N. Cornfield for his help with the management of these patients, and the E. B. Hutchinson Trust for their generous financial support.

References

1. Veronesi U, Pizzocaro G. Breast cancer in women subsequent to cystic disease of the breast. *Surg Gynecol Obstet* 1968: 529–32.
2. Davis HD, Simons M, Davis JB. Cystic disease of the breast: relationship to carcinoma. *Cancer* 1964; **17**: 957–78.
3. Haagensen CD, Bodian C, Haagensen DE. *Breast Carcinoma, Risk and Detection*. London: Saunders, 1981.
4. Dogliotti L, Orlandi F, Torta M *et al.* Cations and dehydroepiandrosterone-sulfate in cyst fluid of pre- and menopausal patients with gross cystic disease of the breast. Evidence for the existence of subpopulations of cysts. *Eur J Cancer Clin Oncol* 1986; **22**: 1301–7.
5. Dixon JM, Scott WN, Miller WR. Natural history of cyst disease: importance of cyst type. *Br J Surg* 1985; **72**: 190–2.
6. Miller WR, Dixon JM, Scott WN, Forrest APM. Classification of human breast cysts according to electrolyte and androgen conjugate composition. *Clin Oncol* 1983; **9**: 227–32.
7. Dixon JM, Miller WR, Scott WN, Forrest APM. The morphological basis of human breast cyst populations. *Br J Surg* 1983; **70**: 604–6.
8. Dixon JM, Miller WR, Yap PL, Scott WN, Forrest APM. Further studies on human breast cyst fluids. *Br J Surg* 1983; **70**: 684.
9. Dixon JM, Lumsden AB, Miller WR. The relationship of cyst type to risk factors for breast cancer and the subsequent development of breast cancer in patients with breast cystic disease. *Eur J Cancer Clin Oncol* 1985; **21**: 1047–50.
10. Page DL, Dupont WD. Are breast cysts a premalignant marker? *Eur J Cancer Clin Oncol* 1986; **22**: 635–6.
11. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; **312**: 146–51.
12. Dixon JM, Scott WN, Miller WR. An analysis of the content and morphology of human breast microcysts. *Eur J Surg Oncol* 1985; **11**: 151–4.

Paper accepted 5 January 1988

Case report

Br. J. Surg. 1988, Vol. 75, July, 704

Artefactual body wall ecchymosis in acute pancreatitis

C. Wilson

Division of Surgery, Royal Infirmary,
Glasgow G4 0SF, UK
Correspondence to: Mr C. Wilson

Grey Turner's and Cullen's signs are unusual cutaneous stigmata of intra-abdominal disease, most frequently seen complicating acute pancreatitis. Marked bruising, centred on the umbilicus but extending in a patchy fashion over the abdominal wall, was first noted in a 37-year-old man 11 days after admission with acute alcoholic pancreatitis. Diagnostic paracentesis had earlier resulted in a small area of bruising below the umbilicus. After featuring as a short case in the Surgical Fellowship examination when other possible sites of bruising were discussed within earshot, he developed bruising of the left flank (*Figure 1*) and 2 days later on the right. Another patient subsequently informed the nursing staff that this man had been repeatedly striking his abdomen and sides with a hairbrush while in bed (out of sight of the nursing station) and while in the toilet area. This was later confirmed by the nursing staff.

The bruising was self-inflicted and in retrospect the delayed onset and atypical appearance (patchy abdominal wall bruising and low distribution on the flanks, maximal just above the iliac crests) should have aroused our suspicions earlier. In 23 patients bruising was never observed to occur after the first week of illness[1]. Artefactual ecchymosis should be considered amongst the other reported causes of abdominal wall bruising.

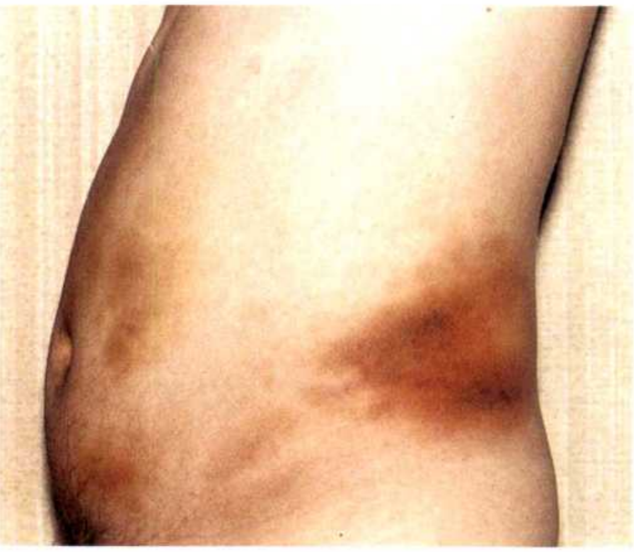


Figure 1 *View of left flank showing marked bruising, maximal just above the iliac crest, and also patchy bruising over the anterior abdominal wall*

Acknowledgements

Thanks to Mr C. W. Imrie for permission to report his case.

References

1. Dickson AP, Imrie CW. The incidence and prognosis of body wall ecchymosis in acute pancreatitis. *Surg Gynecol Obstet* 1984; **159**: 343–7.

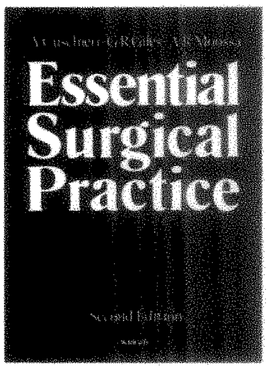
Paper accepted 19 December 1987

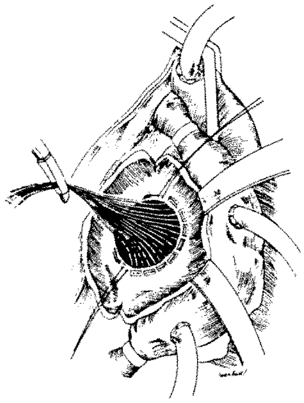
New from WRIGHT

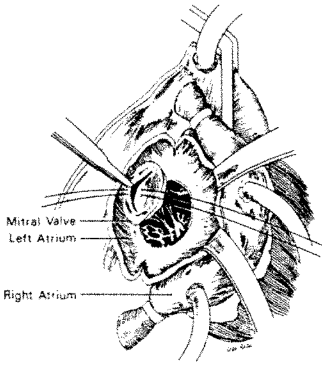
Essential Surgical Practice

Second Edition

Edited by
A Cuschieri MD ChM FRCS(Eng) FRCS(Edin)
Professor and Head of Department of Surgery, University of Dundee, Ninewells Hospital, Dundee, UK
G R Giles MD FRCS
Professor and Head of Department of Surgery, St James's University Hospital, Leeds, UK
A R Moossa MD FRCS(Eng) FRCS(Edin) FACS
Professor of Surgery and Chairman of the Department of Surgery, University of California, San Diego; Surgeon-in-chief, University of California Medical Center, San Diego, California, USA







★ Second edition of this classic systematic and comprehensive surgical textbook ★ Thoroughly revised and completely up-to-date ★ The section on cardiac surgery has been rewritten and to reflect its increasing importance there is a completely new section on the specialty of trauma surgery ★ Over 100 new illustrations ★ Comprehensively indexed ★ Many references for further reading

The second edition of this classic surgical textbook for postgraduate students has been thoroughly revised and updated to reflect the most recent advances and developments. The cardiac surgery section has been completely rewritten under new authorship and there is an entirely new section on trauma, rapidly emerging as a separate surgical specialty. All other chapters have been extensively revised or rewritten to bring them completely up-to-date.

Reviews of the First Edition

'This book is highly readable and is a real contribution to surgical education.' *Archives of Surgery*

'It should be a great success on both sides of the Atlantic.' *Annals of the Royal College of Surgeons*

'. . . Covers very well an extensive range of material which is well illustrated and readily comprehensive. It should be very useful equipment for the trainee surgeon for the Australasian college.' *New Zealand Medical Journal*

Concise Contents: General surgical aspects • Trauma • Head and neck surgery • Neurosurgery • Thoracic surgery • Cardiac surgery • Vascular surgery • General surgery • Genito-urinary surgery

April 1988 1456 pages 272 x 210mm Hardcover Illustrated – 604 line and 891 halftones
0 7236 0861 X £50.00

Order this title from your usual bookseller or complete the coupon below.

ORDER FORM

To: **IOP Publishing, 7 Great Western Way,**
Bristol BS1 6HE, UK.
Telephone: (0272) 292151
Telex: 449907 STONEB G

Cash or credit card details with order are essential

Please send me ________ copy(s) of Essential Surgical Practice, Second Edition 0 7236 0861 X at £50.00.

Please select preferred method of payment:
☐ I enclose remittance for £ ________________
Cheques should be made payable to IOP Publishing Ltd

☐ Please debit my credit card as follows
☐ Access ☐ American Express ☐ Diners Club
☐ Barclay and other Visa cards
Your account will be drawn by IOP Publishing Ltd.

Card Number ________________
Expiry Date ________ Signature ________

Name ________________
Position ________________
Address ________________
____
Postcode ________

Registered office: 88 Kingsway, London WC2B 6AB.
Company registered in England. Registered number 125354.

Wright
an imprint of Butterworths

NEW

Contemporary Reviews in Obstetrics and Gynaecology

Editors: **Geoffrey Chamberlain** and **James Owen Drife**

ISSN 0953-9182 Published three times per annum

★ SPECIAL INTRODUCTORY OFFER ★

- Volume One will contain four issues for the price of three
- 10% discount for individual subscribers placing their subscription by 31st December 1988
- 1st Issue Published September 1988

For further details please contact Jane Waters at Butterworth Scientifc Ltd, PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK.

Please send me further details on Contemporary Reviews in Obstetrics and Gynaecology
Name
Organization
Address
Date

Butterworths
meeting professional needs

New from WRIGHT . . .

Logan Turner's Diseases of the Nose, Throat and Ear · Tenth Edition

A G D Maran MB ChB MD FRCS(ED) FACS
Head of the Department of Otolaryngology, University of Edinburgh and Consultant Otolaryngologist, Royal Infirmary and City Hospital, Edinburgh

★ Tenth edition ★ Updated and expanded – new section on paediatric otolaryngology, rhinology section re-written ★ New illustrations

Contents: THE NOSE: Anatomy and physiology • Investigation of nasal disease • Nasal and facial trauma • Epistaxis • Acute rhinosinusitis • Chronic rhinitis • Chronic sinusitis • Allergic rhinitis and nasal polyps • Benign tumours • Facial pain • Cosmetic facial surgery • Trans-sphenoidal hypophysectomy • HEAD AND NECK • Anatomy of the pharynx • Investigation of pharyngeal disease • Infections of the pharynx • Benign disease of the pharynx: Neck space infections • Tumours of the nasopharynx • Tumours of the oropharynx • Tumours of the oral cavity • Salivary gland disease • Anatomy of the larynx • Investigation of laryngeal disease • Voice problems • Laryngeal infections • Rare laryngeal tumours • Cancer of the larynx • Vocal cord paralysis • Laryngotracheal trauma • Tracheostomy • Neck masses • Cancer of the nose and sinuses • Tumours of the ear • THE EAR: Anatomy and physiology • Investigation of ear disease • Audiology and vestibulometry • Disease of the external ear • Acute otitis media in adults • Chronic otitis media • Extracranial complications of the otitis media • Intracranial complications of otitis media • Otosclerosis • Sensorineural deafness • Tinnitus • Vertigo • Cerebello pontine angle tumours • Otologic trauma • The facial nerve • PAEDIATRICS: Tonsils and adenoids • The catarrhal child • Laryngeal stridor • Endoscopy • Intubation and tracheostomy • Subglottic stenosis • Tumours of the head and neck • Deafness in children • Acute ostitis media and mastoiditis • Secretory otitis media

November 1987 464 pages 234 × 156mm Softcover Illustrated – 153 line and 52 half-tones
0 7236 0945 4 £14.95

Please order this title from your usual bookseller – or in case of difficulty from
Stonebridge Distribution Ltd, 7 Great Western Way, Bristol, BS1 6HE
Telephone: 0272 292151

Butterworths/Wright **John Wright – an imprint of Butterworths**

Br. J. Surg. 1988, Vol. 75, July,
705–707

Effect of vertical banded gastroplasty on the natural history of gastritis in patients with morbid obesity: a follow-up study

J.-F. Flejou,
E. R. T. C. Owen*,
A. C. Smith† and
A. B. Price

Departments of Pathology,
**Surgery and †Gastroenterology,*
Northwick Park Hospital and
Clinical Research Centre, Harrow,
UK

Correspondence to: Dr A. B. Price,
Department of Pathology,
Northwick Park Hospital, Watford
Road, Harrow, Middlesex
HA1 3UJ, UK

Vertical banded gastroplasty is an accepted surgical treatment for morbid obesity. The aim of this study was to evaluate its effect on the natural history of gastritis, as the occurrence of gastritis and dysplasia have been reported after gastric bypass, another type of bariatric surgery. Thirty-four patients who underwent vertical banded gastroplasty between 1983 and 1987 were studied, and the follow-up varied from 1 to 47 months (mean 22 months). We found no increase of gastritis and intestinal metaplasia after surgery, and we did not observe any case of gastric dysplasia. Only one patient with pre- and postoperative specimens showed a deterioration in gastric histology after surgery, and this was of a minor degree. These initial results are encouraging for surgeons interested in the treatment of morbid obesity.

Keywords: Gastroplasty, gastritis, morbid obesity

Vertical banded gastroplasty and gastric bypass surgery have replaced intestinal bypass as treatment for morbid obesity[1]. They are now accepted as efficient and safe procedures, although some short-term complications, such as leakage, infection, thrombosis and stomal stenosis, are well described in the literature[2,3]. After gastric bypass, the occurrence of gastritis and dysplasia have been reported[4–7] but the long-term physiological and pathological consequences of bariatric surgery are still unknown. Because of the probable long-term pre-malignant complications of gastrectomy, data on this subject are important. Such studies have not been carried out after vertical banded gastroplasty as the procedure was described only 6 years ago. The purpose of this (part retrospective, part prospective) study was to investigate the gastric pathology in patients before they underwent vertical banded gastroplasty and then to observe the effects of the procedure on the gastric mucosa at follow-up endoscopic examination. The results presented here represent an interim report of a continuing long-term study.

Patients and methods

A total of 34 patients who underwent vertical banded gastroplasty (*Figure 1*) and at least one endoscopy with biopsy between 1983 and 1987 were included in the study. There were 33 female and 1 male patients, aged 19–58 years (mean 38·7 years). None of the patients had a previous history of gastrointestinal disease, but four complained of 'heartburn'. The number of endoscopic examinations and their time in relation to surgery is shown in *Table 1*. From the total number of 34 patients, 13 had both pre- and postoperative endoscopy and biopsy, 9 had only pre-operative biopsies and 12 had only postoperative biopsies. Postoperative biopsy was carried out 1–47 months after surgery (mean 22 months). All endoscopic examinations were performed by the same endoscopist.

Tissue was fixed in neutral unbuffered formalin, embedded in paraffin, and sectioned at $3\,\mu m$. The specimens were stained with haematoxylin and eosin. The presence of chronic gastritis was assessed using Whitehead's classification[8] after a semiquantitative evaluation of the lymphoid cell infiltrate in the lamina propria and the glandular atrophy (0, absent; +, mild; + +, moderate; + + +, severe). The same evaluation was done for the presence of oedema in the lamina propria, polymorphonuclear cells in the epithelium and in the lamina propria, intestinal metaplasia and dysplasia. The biopsies were read by two pathologists (J.-F.F., A.B.P.), each unaware of the other's opinion. The few differences were resolved by subsequent discussion.

Results

In contrast to the histological findings, no macroscopic abnormalities were seen on endoscopy, but microscopy revealed chronic gastritis present in the antrum and/or body mucosa in 10 of 22 patients before surgery. Three had foci of intestinal metaplasia. Chronic gastritis was observed in 11 of 25 patients after surgery (*Figure 2*). One showed intestinal metaplasia. In only 13 patients was a direct comparison between pre- and postoperative status possible (*Table 2*); in these 13 patients the mean follow-up period was 15 months, the range 6–24 months. However, in only one patient was there a change of pattern, this being from normal body to mild atrophic gastritis at 18 months; this patient did have mild antral atrophic gastritis before surgery. Eighteen patients had postoperative biopsies which allowed a comparison between the proximal gastric pouch and the distal body; the only histological difference was that of superficial oedema in the proximal pouch in twelve. Dysplasia was never found in any biopsy and there was no case of acute gastritis. The only differences between the two pathologists'

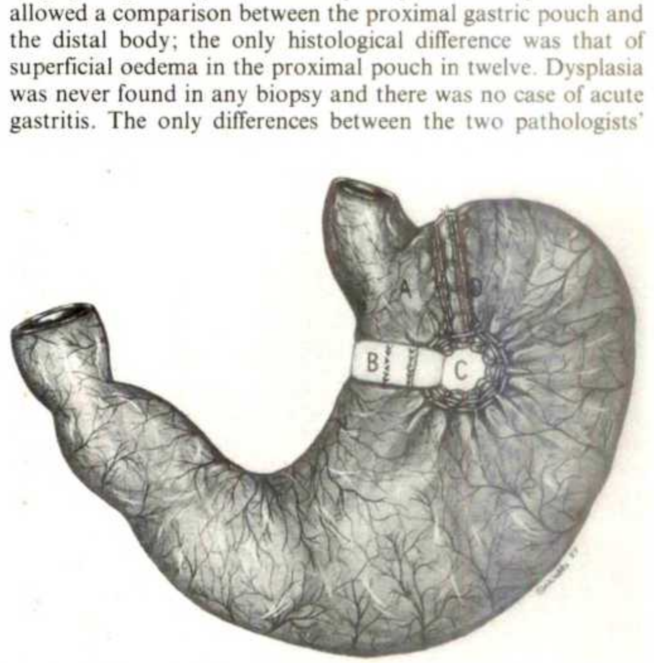


Figure 1 *Drawing of a vertical banded gastroplasty showing a small pouch (A), an outlet band (B), a gastric window (C), and the vertical double-stapled line (D). (Courtesy of Nigel Webb)*

0007–1323/88/070705–03$3.00 © 1988 Butterworth & Co (Publishers) Ltd

Table 1 *Number of patients studied*

Patients	Before surgery	After surgery
Patients with only body biopsy	3 (3)	6 (9)
Patients with body and antrum biopsies	19 (19)	19 (34)
Total	22 (22)	25 (43)

Number of endoscopic examinations in parentheses

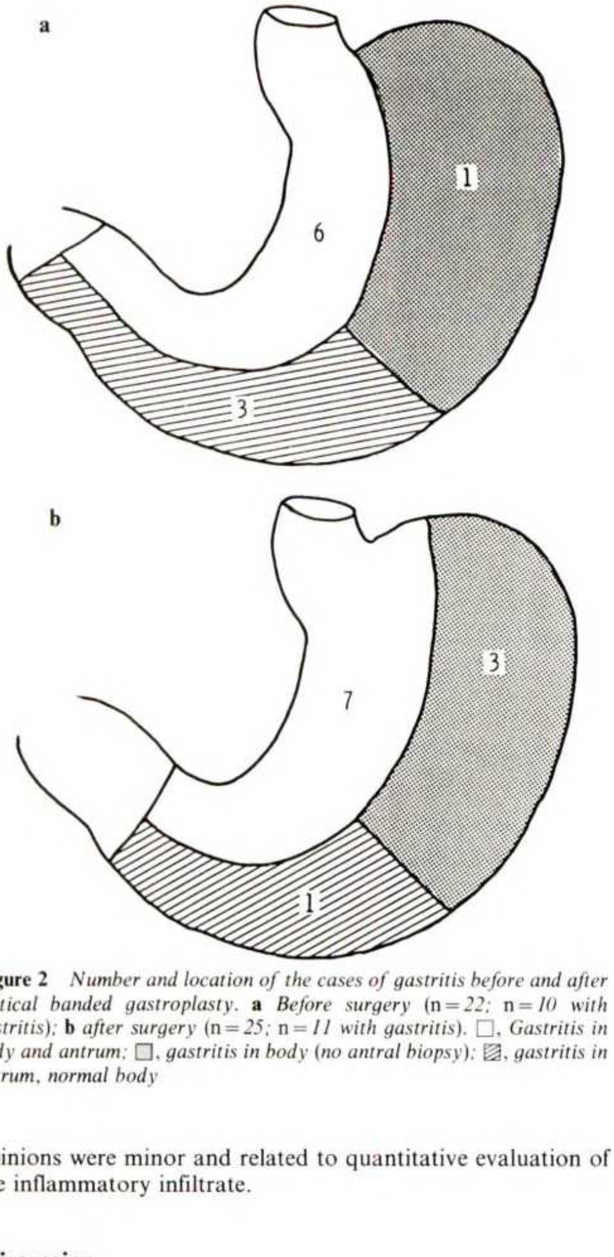


Figure 2 *Number and location of the cases of gastritis before and after vertical banded gastroplasty.* **a** *Before surgery* (n = *22;* n = *10 with gastritis);* **b** *after surgery* (n = *25;* n = *11 with gastritis).* □, *Gastritis in body and antrum;* ▩, *gastritis in body (no antral biopsy);* ▨, *gastritis in antrum, normal body*

opinions were minor and related to quantitative evaluation of the inflammatory infiltrate.

Discussion

Persistent severe obesity produces considerable morbidity and is refractory to non-surgical methods in the majority of cases: this is the reason for the current development of various surgical procedures, among which gastric bypass operations and vertical banded gastroplasty have become the most popular. Vertical banded gastroplasty was described by Mason[9] in 1982 and, unlike the horizontal surgery of gastroplasty, has been shown to be effective. Descriptions of the short-term complications attributable to surgery are known and this was not the aim of this study. Obese patients are usually young with no history of gastric disease. It is important to evaluate the middle- and long-term effects of these surgical procedures on the gastric mucosa in these individuals, particularly as partial gastrectomy for peptic ulcer disease is a precancerous condition. Such data have not been reported after vertical banded gastroplasty, and the first results provided here are encouraging. Before surgery, 41 per cent of our patients had some form of chronic gastritis in the antral mucosa and 32 per cent in the body mucosa. This high incidence of gastritis can be compared with the result of 30 per cent in the series of obese patients assessed before surgery by Flickinger *et al.*[7], and the incidence of 36 per cent found by Kreuning *et al.* in young healthy individuals[10]. The figures suggest that the incidence of chronic gastritis is no different in obese patients from that in the general population.

Table 2 *Histology of the gastric mucosa in 13 patients with pre- and postoperative biopsies*

Location	Histological findings	No. of patients	
		Before surgery	After surgery
Body (13 patients)	Normal mucosa	10	9
	Superficial gastritis	3	3
	Mild atrophic gastritis	0	1
Antrum (7/13 patients)	Normal mucosa	5	5
	Mild atrophic gastritis	1	1
	Moderate atrophic gastritis	1	1

Our own patients did not show any change in the incidence of chronic gastritis before and after surgery, and some patients have now been followed up for up to 47 months (mean 22 months). Furthermore, only one of thirteen patients with pre- and postoperative biopsies had a histological change of status: this was minor and within the body mucosa. After surgery we did not find any increase in the occurrence of intestinal metaplasia or any cases with dysplasia. As part of a wider study on *Campylobacter pylori* in gastric mucosa, the biopsies of the 34 patients in this study were also examined for these organisms[11]. There was no evidence that the gastric manipulation of vertical banded gastroplasty increased susceptibility to gastric infection by *C. pylori*.

Unlike gastroplasty, gastric bypass is a major diversionary procedure which suppresses food entrance into the stomach. As this is one of the mechanisms determining gastric secretion, atrophic changes can be expected after a bypass, and have been shown in animal models: by histology in rats[12] and by electron microscopy in dogs[13]. Such animal models have not been reported on gastroplasty. After gastric bypass, a high percentage of chronic gastritis has been found[4] and attention has recently been drawn to these results[14]. Even more alarming, MacCarthy *et al.*'s study[4] found a high incidence of gastric dysplasia after surgery. However, in our opinion, these results can be questioned because there was no assessment of the pre-operative histological status, and the criteria used to diagnose gastric dysplasia are not those in accepted use[15]. Dysplasia is a serious condition: its relationship to carcinomas is well established and both lesions have been shown to be long-term complications of partial gastrectomy[16]. Our study demonstrates that vertical banded gastroplasty does not accelerate the long natural history of chronic gastritis[17], and, within the confidence limits of the follow-up period of the study, does not provoke gastric dysplasia.

The findings in this paper are encouraging for surgeons interested in the treatment of morbid obesity. However, there is still a need for a long-term programme to monitor the gastric mucosal changes in patients after bariatric surgery for, after partial gastrectomy, dysplasia and cancer can take up to 20 years or more to become evident.

At this stage it would seem reasonable from the data in this study to suggest that patients should have a pre-operative endoscopy to establish the base-line pathology of their gastric mucosa. Follow-up endoscopy, unless indicated for symptomatic reasons, then appears unnecessary for 2 years.

After this, and until additional data accrue, further endoscopies are advisable at 5 years and 10 years. This will obviously be modified by subsequent experience.

Acknowledgements

J.-F. Flejou acknowledges the help of a British Council grant, and we acknowledge the help of the endoscopy unit at Northwick Park Hospital.

References

1. Griffen WO, Bivins BA, Bell RM The decline and fall of the jejunoileal bypass. *Surg Gynecol Obstet* 1983; **157**: 301–8.
2. Dietel M, Jones BA, Petrov I *et al.* Vertical banded gastroplasty: results in 233 patients. *Can J Surg* 1986, **29**: 322–4.
3. Eckhout GV, Willbanks OL, Moore JT. Vertical ring gastroplasty for morbid obesity. Five year experience with 1,463 patients. *Am J Surg* 1986; **152**: 713–16.
4. MacCarthy HB, Rucker RD, Chan EK *et al.* Gastritis after gastric bypass surgery. *Surgery* 1985; **98**: 68–71.
5. Flickinger EG, Sinar DR, Pories WJ, Sloss RR, Park HK, Gibson JH. The bypassed stomach. *Am J Surg* 1985; **149**: 151–6.
6. Park HK, Sinar DR, Sloss RR, Whitley TW, Silverman JF. Histologic and endoscopic studies before and after gastric bypass surgery. *Arch Pathol Lab Med* 1986; **110**: 1164–7.
7. Flickinger E, Sinar D, Silverman J, Park K, Gibson J, Swanson M. The effect of gastric bypass on gastric mucosa: a prospective analysis. *Int J Obes* 1987; **11**: 208.
8. Whitehead R. Simple (non specific) gastritis In: *Mucosal Biopsy of the Gastrointestinal Tract*, 2nd edn. Philadelphia· Saunders, 1985: 33–58.
9. Mason EE. Vertical banded gastroplasty for obesity *Arch Surg* 1982; **117**: 701–6.
10. Kreuning J, Bosman FT, Kuiper G, Van Den Wal AM, Lindeman J. Gastric and duodenal mucosa in 'healthy' individuals. An endoscopic and histopathological study of 50 volunteers. *J Clin Pathol* 1978; **31**: 69–77.
11. Flejou JF, Price AB, Smith AC, Owen ERTC. *Campylobacter pylori* and gastric manipulation for morbid obesity. *Lancet* 1988; **ii**: 917–8.
12. Young EA, Taylor MM, Taylor MK, MacFee AS, Lawayne Miller O, Gleiser CA. Gastric stapling for morbid obesity: gastrointestinal response in a rat model. *Am J Clin Nutr* 1984; **40**: 293–302.
13. Sinar DR, Flickinger EG, Harvell JC, Foil MB. Physiologic and histologic consequences of gastric bypass surgery in a dog model. *Gastroenterology* 1984; **86**: 1253.
14. Gazet JC, Pilkington TRE. Surgery of morbid obesity. *Br Med J* 1987; **295**: 72–3.
15. Morson BC, Sobin LH, Grundmann E *et al.* Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol* 1980; **33**: 711–21.
16. Domellof L, Eriksson S, Janunger KG. Carcinoma and possible precancerous changes of the gastric stump after Billroth II resection. *Gastroenterology* 1977, **73**: 462–8.
17. Siurala M, Isokoski M, Varis K, Kekki M. Prevalence of gastritis in a rural population. Bioptic study of subjects selected at random *Scand J Gastroenterol* 1968, **3**. 211–23.

Paper accepted 11 January 1987

Br. J. Surg. 1988, Vol. 75, July, 708–712

Treatment of stomach cancer, a national experience

B. Valen, A. Viste, T. Haugstvedt, G. E. Eide, O. Søreide and Members of the Norwegian Stomach Cancer Trial*

The Norwegian Stomach Cancer Trial, Department of Surgery and Section for Medical Informatics and Statistics, University of Bergen, Haukeland sykehus, Norway
Correspondence to: Dr O. Søreide, Department of Surgery, University of Bergen, N-5021 Haukeland sykehus, Norway

A total of 1165 patients with stomach cancer were entered into a prospective, observational national study. They represented 54 per cent of all stomach cancer patients reported to the Cancer Registry in Norway during the study period, and data are analysed for three hospital levels (local, county and university hospitals). The median age was 71 years (range 18–96 years). The median pretreatment delay was 113 days, and 46 per cent of patients had a performance status (Karnofsky index) of $\leqslant 80$. The diagnosis was confirmed by pre-operative histology in 88 per cent of cases. In all, 88 per cent of patients underwent surgery, the resectability rate was 67 per cent and 50 per cent had a potential curative operation. Total gastrectomy was most commonly performed. Lymph node dissection was performed in 14 per cent of those undergoing a curative resection. The postoperative complication rate was 27 per cent but varied with the type of operation, being highest in proximal resection (55 per cent) and lowest after distal resection (19 per cent). A total of 7 per cent of the patients died postoperatively. Most patients had advanced disease at the time of treatment and only 6 per cent had stage I tumours. There were significant differences in patient and treatment characteristics between the three hospital levels. In conclusion, patient selection bias which will influence results does occur. A fairly aggressive attitude towards local disease was found, but the low proportion of patients undergoing lymph node dissection not only leads to questions regarding the efficacy of this treatment policy, but also casts doubt on the validity of staging of stomach cancer. Morbidity and mortality rates are still high. The consequences of the differences revealed between hospital groups are difficult to interpret. Proponents of both regionalization of treatment and small hospital care may find arguments for their case in the data.

Keywords: Gastric cancer, treatment

Despite a decreasing incidence worldwide, stomach cancer is still the second commonest form of cancer among men and the third among women[1]. A striking phenomenon when reviewing the literature has been the apparent conflict between results published by Japanese and western authors with regard to patient characteristics, diagnosis, treatment, staging and survival[2–7]. Whereas cancer treatment has been standardized in Japan[8], such standardization has not been achieved in the West. In the western literature most papers are based on experience from single institutions. National data allowing direct comparison with Japanese results have not been published.

Hospital selection bias in cancer treatment occurs. Consequently, multi-institutional and national data are needed but are rarely available. With regard to stomach cancer, epidemiological data from Norway suggest that there has been a shift in staging towards less advanced disease over the last 15 years[9]. However, treatment results are not available. To overcome some of the problems alluded to above and, in particular, the need for more reliable national data, we initiated and conducted a national study on stomach cancer treatment. The results presented here give the analyses of the clinical part of the study

Patients and methods

The trial was initiated by the Department of Surgery, University Hospital, Bergen, Norway and conducted in co-operation with 51 other hospitals operating at three levels (local, county and university hospitals) and the Cancer Registry of Norway. Patient accrual started on 1 September 1982 and the study closed on 31 December 1984, at which time 1165 patients (705 men (60·5 per cent) and 460 women (39·5 per cent)) had been entered. They comprised 54 per cent of all stomach cancer patients registered by the Cancer Registry during this period

The trial was organized as an observational, multicentric and prospective study. The study protocol did not require standardization of investigative strategy or of treatment. However, detailed information regarding pre-, per- and postoperative investigations and treatment was recorded on data sheets by a principal investigator in each hospital and submitted to the study headquarters. Tissue specimens were examined by participating pathologists Staging of the tumours was performed according to the TNM classification[10].

All data were recorded and analysed using the BMDP[11] statistical package. Student's t test (unpaired, two-tailed) and χ^2 test were used for the statistical analyses as appropriate.

Results

Pre-operative characteristics

The median age of the patients was 71 years. Women were significantly older than men (71 *versus* 68 years, $P = 0{\cdot}002$). Median pretreatment delay, defined as the time interval from onset of symptoms to treatment, was 113 days.

The patients' general clinical status classified according to the Karnofsky index[12] was a median of 90 (*Table 1*). The Karnofsky index reflected the type of treatment which could be given, as a high index seemed to be a prerequisite for curative resection (*Table 1*). The Karnofsky index also correlated with

---

* The participating surgical departments are given in the appendix

0007-1323/88/070708-05$3 00

Table 1 *Pre-operative Karnofsky index and its relation to treatment in 1013 patients*

Karnofsky index	All patients*	Curative resection†	Palliative resection or inoperable†
90–100	544 (54)	352 (65)	192 (35)
60–80	316 (31)	132 (42)	184 (58)
50–60	95 (9)	29 (31)	66 (69)
10–40	58 (6)	5 (9)	53 (91)

Values in parentheses are percentages calculated from *column or †row totals

Table 2 *Treatment of 1165 stomach cancer patients*

	Total* ($n = 1165$)	Curative resection† ($n = 583$)
Resection ($n = 781$)		
Total gastrectomy	358 (31)	286 (80)
Distal resection	239 (21)	164 (69)
Subtotal gastrectomy	154 (13)	117 (76)
Proximal resection	30 (3)	16 (53)
Non-resectional surgery ($n = 244$)		
Gastrojejunostomy	70 (6)	
Intubation	13 (1)	
Gastrostomy	4	
Explorative laparotomy	157 (13)	
No operation	140 (12)	

Values in parentheses are percentages calculated from *column or †row totals

weight loss ($P = 0.002$, low index with excess weight loss) and age ($P < 0.001$, low index in the oldest patients).

A total of 114 patients (11 per cent) had cancer in a stomach previously resected for benign disease (stump cancer). We found no differences in Karnofsky index, age or sex for patients previously resected *versus* those not resected.

The diagnosis was confirmed by pre-operative histology in 88 per cent of the patients. The proportion of patients with a tissue-proven diagnosis before treatment varied significantly between the hospital groups (*Table 8*; see later).

Type of treatment

The treatment given is shown in *Table 2*. A total of 1025 (88 per cent) patients underwent surgery and 781 (67 per cent) had their tumour resected. Resected patients were significantly younger than unresected (mean 68 *versus* 71 years, $P < 0.001$) and in better general condition (mean Karnofsky index 89 *versus* 72, $P < 0.001$).

In all, 583 patients (57 per cent of those undergoing surgery, 50 per cent of all patients) underwent a potentially curative resection, i.e. no residual macroscopic tumour and clear resection margins. Of the remaining 198 resected patients, 182 (16 per cent of all patients) underwent a palliative resection, whereas the type of operation (curative or palliative) was not stated for 16 patients. A total of 384 patients underwent non-resectional surgery or were not operated on, of whom 321 were classified as unresectable; information was not given for the remaining 63 patients. Of the 358 patients treated with total gastrectomy, this procedure was necessitated (i.e. in the operating surgeon's judgement) by the location of the tumour in 69 per cent of cases (247 out of 358).

When stump cancer patients were compared with those previously unresected, we found no differences in resectability or resection for cure rate (data not given).

Resection of other structures in addition to the gastric resection is outlined in *Table 3*. Resection of the greater and lesser omentum was performed in most patients, whereas lymph node dissection was carried out infrequently.

Of 823 anastomoses performed to re-establish gastrointestinal tract continuity, 508 (62 per cent) were hand-sewn and 315 (38 per cent) performed using a stapling device. Oesophagojejunostomy after total gastrectomy was constructed using a stapling device in 75 per cent of the patients (for detailed results see Reference 13).

Complications and postoperative mortality

Postoperative complications were recorded in 276 patients (27 per cent of those who underwent surgery). General complications (pulmonary, cardiovascular, etc.) were most common (*Tables 4* and *5*). Proximal resection carried the highest rate both for lethal and non-lethal complications (*Table 5*).

Anastomotic insufficiency was seen in 6 per cent (43 out of 781) of those undergoing resection. In 41 of these patients leakage was ascertained by radiographic contrast studies, and in the remaining 2 patients by the presence of an enterocutaneous fistula.

Enterocutaneous fistulae developed in 13 patients (2 per cent). Wound infection (i.e. serosanguineous or purulent discharge and a positive culture of a pathogen from the discharge) was seen in 4 per cent (37 out of 1025). Postoperative haemorrhage (i.e. a significant fall in haemoglobin concentration necessitating blood transfusion) occurred in 25 patients (2 per cent).

Compared with an abdominal operation, thoracolaparotomy carried a significantly higher risk of complications (45 *versus* 27 per cent, $P = 0.002$). We found no significant

Table 3 *Additional structures resected according to type of treatment for 765 of 781 patients undergoing gastric resection*

Additional structure	Curative resection ($n = 583$)	Palliative resection ($n = 182$)	Total gastrectomy ($n = 358$)
Greater omentum	469 (80)	119 (65)	323 (90)
Lesser omentum	422 (72)	107 (59)	315 (88)
Spleen	208 (36)	53 (29)	229 (64)
Pancreatic tail	34 (6)	13 (7)	41 (12)
Transverse colon	17 (3)	7 (4)	12 (3)
Liver resection	7 (1)	4 (2)	10 (3)
LN, hepatoduodenal ligament	51 (9)	5 (3)	51 (14)
LN, coeliac axis	79 (14)	10 (6)	77 (22)

Values in parentheses are percentages calculated from column totals (n). LN, lymph nodes

Table 4 *Complications in 1025 patients operated on for stomach cancer*

	No. of patients*	No. of deaths†	No. of reoperations†
General complications	177 (17)	64 (36)	14 (8)
Anastomotic insufficiency	43 (6)‡	11 (26)	18 (42)
Septicaemia	42 (4)	20 (48)	13 (31)
Intra-abdominal infection	37 (4)	13 (35)	23 (62)
Enterocutaneous fistula	13 (2)‡	3 (23)	6 (46)
Wound infection	37 (4)	5 (14)	12 (32)
Postoperative haemorrhage	25 (2)	8 (32)	10 (40)
Intestinal obstruction	15 (1)	3 (20)	10 (67)
Wound dehiscence	12 (1)	1 (8)	7 (58)
Total	276 (27)	75 (7)*	54 (5)*

Values in parentheses are percentages calculated from the following totals: *all patients operated on; †those with the complication, ‡those having a resection. Some patients had more than one complication or cause of death

Table 5 *Complications, reoperations and lethality related to operative technique*

		Complication	Reoperation	Deaths*	Total deaths
Curative resections ($n = 583$)					
Total gastrectomy	($n = 286$)	107 (37)	30	7	21 (7)
Distal resection	($n = 164$)	34 (21)	3	0	11 (7)
Subtotal gastrectomy	($n = 117$)	31 (27)	4	1	10 (9)
Proximal resection	($n = 16$)	9 (56)	3	1	4 (25)
Palliative resections ($n = 182$)					
Total gastrectomy	($n = 65$)	27 (41)	2	0	6 (9)
Distal resection	($n = 70$)	10 (14)	1	0	5 (7)
Subtotal gastrectomy	($n = 34$)	11 (32)	5	2	5 (15)
Proximal resection	($n = 13$)	7 (54)	0	0	1 (8)
Others ($n = 227$)					
Gastrojejunostomy	($n = 70$)	16 (23)	3	0	7 (10)
Explorative laparotomy	($n = 157$)	21 (13)	3	1	5 (3)

* The number who died after the reoperation. Values in parentheses are percentages calculated from the total number of patients having the specified treatment

Table 6 *Tumour location related to resectability and presumed curability*

Location	Total* ($n = 1079$)	Resected† ($n = 751$)	Resected for cure‡ ($n = 572$)
Fundus	193 (18)	128 (66)	100 (52)
Fundus and corpus	110 (10)	61 (55)	44 (40)
Corpus (midstomach)	102 (9)	86 (84)	73 (72)
Corpus and antrum	128 (12)	95 (74)	64 (50)
Antrum	369 (34)	309 (84)	246 (67)
All regions	177 (16)	72 (41)	45 (25)

The location of the tumour in 86 patients is not stated. Values in parentheses are percentages calculated from the following totals: *column total; †regional (row) total (location of tumour not stated for 30 patients); ‡regional (row) total (location of tumour not stated for 11 patients)

Table 7 *Tumour staging according to the TNM classification system*[10]

	Total*	Resected†	Resected† for cure
Stage I	74 (6)	74 (100)	74 (100)
Stage II	159 (14)	159 (100)	150 (94)
Stage III	194 (17)	194 (100)	163 (84)
Stage IV	452 (39)	241 (53)	112 (25)
Not stated	286 (24)	113 (40)	84 (29)
Total	1165	781 (67)†	583 (50)†

Values in parentheses are percentages calculated from *column or †row totals

Table 8 *Differences between hospital levels*

	University hospital ($n = 471$)	County hospital ($n = 270$)	Local hospital ($n = 423$)	P value
Sex (male)	62	58	61	n.s
Age >70 years	46	49	56	0·02
Karnofsky >80	64	61	37	<0·001
Stump cancer	12	6	11	0·04
Histology pre-operatively	91	86	81	0·001
Resected tumour	70	63	67	0·17
Potential curative resection	55	52	53	n.s.
Total gastrectomy	44	24	21	<0·001
Thoraco-laparotomy	8	7	3	0·03
Complications	26	16	28	0·001
Lethal complications	5	6	11	0·003
Reoperations	5	4	6	n.s.
Stapling used	53	35	23	<0·001
Prophylactic antibiotic given	68	58	49	<0·001

Values are percentages

differences in frequency of reoperation (8 *versus* 5 per cent) or lethal complications (13 *versus* 7 per cent).

The overall frequency of reoperation was 5 per cent (54 out of 1025), 7 per cent for those with a curative resection, 4 per cent for those undergoing palliative surgery and 3 per cent for non-resectional surgery ($P = 0·001$). Proximal resection and total gastrectomy had the highest rate of reoperation (10 and 9 per cent respectively). Twelve patients were reoperated on because of incomplete resection (tumour in the resection margin on final histology).

Postoperative mortality rate (defined as all in-hospital deaths irrespective of whether the patient died before or after 30 days[33]) was 7 per cent (*Table 4*). Of the 54 patients having reoperation, 12 (22 per cent) died (*Table 5*) as did 2 out of 12 patients undergoing reoperation due to incomplete resection.

Patients undergoing potentially curative surgery and those treated by palliative resection were equally affected by non-lethal (31 *versus* 30 per cent, *Table 5*) as well as by lethal complications (8 *versus* 9 per cent respectively).

Tumour location

The location of the tumours is given in *Table 6*. Infiltration of the oesophagus occurred in 11 per cent of the patients, and in 6 per cent the duodenum was affected. Tumours of the antrum and corpus were resected more frequently than tumours at other sites. The resectability rate decreased with increasing extent of the tumour. Staging is given in *Table 7*. Stage I tumours were found in 74 patients (6 per cent).

Patient and treatment characteristics according to hospital group

A total of 471 patients (40 per cent) were treated in university hospitals, 270 (23 per cent) in county hospitals and 423 (36 per cent) were treated in local hospitals. Most patient and treatment characteristics showed highly significant differences between hospital groups (*Table 8*).

Discussion

The results of this national study, comprising 54 per cent of all stomach cancer patients treated in Norway during the study period, lead to several questions and comments First, we confirm that there is selection of patients with regard to type of hospital. As shown in *Table 8*, patients treated in local hospitals were generally older and had a lower performance status than patients treated in other hospitals. This selection may influence both treatment and complication rate as well as survival; the effect on survival is presumably caused by what is described as 'stage migration'[14]. This might explain why some authors report increasing survival rates in patients treated during the last decade whereas cancer registry data show only a modest improvement in overall survival.

Secondly, despite the marked spread of availability of flexible fibre endoscopes in Norway[9], the majority of patients present with extensive (*Table 6*) and advanced disease (*Table 7*) after a fairly long symptomatic period. These data may suggest that significant improvement in treatment results is unlikely to occur despite advances in pre-, per- and postoperative care.

Our data further contrast with results from Japan in that the improved prognosis in Japanese patients is partly related to screening programmes in asymptomatic patients which has resulted in an increasing proportion of patients with early gastric cancer[3,15–17]. Screening for gastric cancer has not been accepted in Norway (or any other western country), but we have seen a rapid expansion of gastroscopy services[9] based on fairly liberal indications. One may argue that the latter policy has not benefited gastric cancer patients[18,19]. That 88 per cent of the patients had a pre-operative confirmed tissue diagnosis merely underlines the fact that pre-operative diagnostic accuracy is not synonymous with improved treatment outcome.

Norwegian surgeons are fairly aggressive with respect to gastric cancer (*Table 2*) as 44 per cent of the patients had a total or subtotal gastrectomy. *Table 6* may, however, suggest that a high proportion of the extended resections were performed as the only possible type of resection ('gastrectomie de nécessité'). In contrast with these findings, *Table 3* shows that lymph node dissection was carried out in relatively few patients, even in those undergoing curative resections. These data—an aggressive surgical attitude towards the stomach cancer itself, but node dissection in only a minority—contrasts with Japanese recommendations[8] and results[20]. Keighley and co-workers[21] as well as others[22,23] have demonstrated the importance of lymph node involvement in determining treatment outcome.

Assessment of lymph nodes by palpation is notoriously difficult[24,25] and without formal node dissection, 'understaging' tends to occur. This makes direct comparison of the results obtained by node dissectors with those obtained when performing resection only an unscientific exercise. Although some authors claim that formal node dissection increases survival[22,26–28], we believe that its main effect is to ensure more accurate staging of the disease.

The problem of staging accuracy also casts serious doubt on the usefulness of the term 'resection for cure'. We feel[29], like the Japanese Research Society for Gastric Cancer[8], that the term should be related to a defined operative procedure, for instance a gastric resection where extensive lymph node dissection has been performed and the distant lymph node station has been found to be tumour-free, and where free resection margins are documented.

The postoperative complication and mortality rates are significantly higher (*Tables 4* and *5*) than those reported in Japanese series[20,30,31], but of the same magnitude as rates published in the western literature[5,6,32]. A full analysis and discussion regarding this problem is beyond the scope of the present paper as detailed data have been published elsewhere[33]. Based on the latter study, as well as others[34], we conclude that age is a decisive factor in determining postsurgical outcome. Consequently, direct comparison with Japanese studies is inappropriate as their patients are younger[2,15].

Detailed analyses of our data[33] have, however, demonstrated that type of operation is a factor which significantly influences complication and mortality rates. Of particular importance are the high rates found in patients treated with proximal resection. The present results may suggest (*Table 5*) that this type of resection is regarded as a 'minor' procedure for patients undergoing palliative resection. Our data[33] show that this type of resection carries prohibitively high postoperative morbidity and mortality rates. Similar conclusions have been made by others[5,7].

The differences in various parameters found between the three hospital levels are of major importance. To our knowledge, comparable data have not been published We wish to emphasize that analyses of the differences between hospital levels are very complicated because of the multifactorial nature of important factors. Results, as presented in *Table 8*, may lead to rapid but unjustifiable conclusions as proponents both for small hospital care and regionalization of surgery for particular diseases may find support for their respective cases in the data. Despite advanced and complicated statistical analyses[33] we are not able to draw firm conclusions. Whereas treatment in specialist centres seems appropriate for subgroups of patients[33], we fully admit that small hospital care, as demonstrated here for the elderly and frail patient, must be correct. Final conclusions cannot be drawn before treatment outcome (i.e. survival) for comparable groups of patients has been studied.

References

1 Parkin DM, Stjernsward J, Muir CS Estimates of the worldwide frequency of the twelve major cancers *Bull World Health Org* 1984, **62**. 163–82.
2 Yamada E, Miyaishi S, Nakazato H *et al.* The surgical treatment of cancer of the stomach. *Int Surg* 1980, **65**: 387–99.
3. Kaneko E, Nakamura T, Uneda N *et al* Outcome of gastric carcinoma detected by gastric mass survey in Japan. *Gut* 1977, **18**. 626–30.
4. Nagato T, Ikeda M, Nakayama F. Changing state of gastric cancer in Japan. *Am J Surg* 1983, **145** 226–33.
5. Inberg MV, Heinonen R, Rantakokka V *et al* Surgical treatment of gastric carcinoma. A regional study of 2590 patients over a 27-year period. *Arch Surg* 1975; **110**. 703–7.
6. Lundh G, Burn JI, Kolig G *et al.* A co-operative international study of gastric cancer. *Ann R Coll Surg Engl* 1974; **54**· 219–28.
7. Adashek K, Sanger J, Longmire WP. Cancer of the stomach. Review of consecutive ten years intervals *Ann Surg* 1979; **189**. 6–10.
8. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery. *Jpn J Surg* 1973, **3**: 61–71.
9 Viste A, Søreide O, Glattre E. Stomach cancer: major trends in incidence during introduction of gastroscopy service in Norway. *Scand J Gastroenterol* 1985; **20**. 99–108
10 Kennedy BJ. TNM classification for stomach cancer *Cancer* 1970; **26**: 971–83
11. Dixon WJ, ed. *BMDP Statistical Software* Berkeley University of California Press, 1985
12 Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents against cancer. In McLeod, ed *Evaluation of Chemotherapeutic Agents* New York Colombia University Press, 1949.
13 Viste A, Eide GE, Søreide O. Stomach cancer: a prospective study of anastomotic failure following total gastrectomy. *Acta Chir Scand* 1987; **153**: 303–6.
14 Feinstein AR, Sosin DM, Wells CK. The Will Rogers Phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *New Engl J Med* 1985; **312**. 1604–8
15. Ohta H, Noguchi Y, Takagi K *et al* Early gastric carcinoma with special reference to macroscopic classification *Cancer* 1987, **60**· 1099–106.
16. Miwa K. Cancer of the stomach in Japan. *Gann* 1979, **22** 61–75.
17. Oshima A, Sakagami F, Haway A *et al.* Evaluation of a mass screening programme for gastric cancer In: Hirayama T, ed

Epidemiology of Stomach Cancer (WHO-CC monograph). Tokyo, 1977: 34–45.

18. Holdstock G, Bruce S. Endoscopy and gastric cancer. *Gut* 1981, **22**: 673–6.
19. Trädgård B, Wehlin L, Lindstrøm C. The yield of endoscopy and double contrast radiography for detection of early gastric cancer in Malmø *Acta Chir Scand* 1980; **146**: 357–62.
20. de Aretxabala X, Konoshi K, Yonemura Y *et al*. Node dissection in gastric cancer. *Br J Surg* 1987; **74**: 770–3.
21. Keighley MRB, Moore J, Roginski C *et al*. Incidence and prognosis of N_4 node involvement in gastric cancer. *Br J Surg* 1984; **71**. 865–6.
22. Douglass AO. Potentially curable cancer of the stomach *Cancer* 1982; **50**: 2582–9
23. Soga J, Kobayashi K, Saito J *et al* The role of lymphadenectomy in curative surgery for gastric cancer *World J Surg* 1979; **3**: 701–8
24. Okajima K. Surgical treatment of gastric cancer with special reference to lymph node removal *Acta Med Okayama* 1977; **31** 369–82
25. Cantrell EG. The importance of lymph-nodes in the assessment of gastric carcinoma at operation *Br J Surg* 1971; **58**: 384–6
26. Nakajima T, Kojitani T. Surgical treatment of gastric cancer with special reference to lymph node dissection. *Diagnosis and Treatment of Gastrointestinal Tumours*. Excerpta Medica, 1981: 207–23.
27. Burmeister R. Long-term survival in cases of early and advanced gastric cancer in Chile *Gann Monograph on Cancer Research* 1986, **31**: 165–70.
28. Kim JP, Jung SE Patients with gastric cancer and their prognosis in accordance with number of lymph node metastases. *Scand J Gastroenterol* 1987; **22** (Suppl 133): 33–5
29. Viste A, Lillestøl J, Søreide O. Cancer of the stomach: are curative resections of any importance with respect to postoperative survival in patients with locoregional disease? *Int Surg* 1984, **69**: 133–5.
30. Fujimaki M, Soga J, Wada K *et al*. Total gastrectomy for gastric cancer. Clinical considerations on 431 cases. *Cancer* 1972; **30**. 660–4
31. Yamada E, Miyaishi S, Nakazato H *et al* The surgical treatment of cancer of the stomach. *Int Surg* 1980: **65**: 387–99.
32. Longmire WP. Gastric carcinoma: is radical gastrectomy worth while? *Ann R Coll Surg Engl* 1980; **62**: 25–30
33. Viste A, Eide GE, Havgstvedt T, Søreide O. Postoperative complications and mortality following surgery for gastric cancer *Ann Surg* 1988; **207**. 7–13
34. Samet J, Hunt WC, Key C *et al* Choice of cancer therapy varies with age of patient. *JAMA* 1986; **255**: 3385–90.

Paper accepted 1 February 1988

Appendix

The Norwegian Stomach Cancer Trial: participating surgical departments

Halden Sykehus (Dr Ø. Hansen); Sentralsykehuset for Østfold (Dr K. Andenes); Sarpsborg Sykehus (Dr S. Skjeldal); Moss Sykehus (Dr C. Wessel-Holst); Sentralsykehuset i Akershus (Dr K. Solheim*); Bærum Sykehus (Dr E. Omland); Rikshospitalet (Dr A. Bergan*); Ullevål Sykehus (Dr Tom Gerner, Dr J Stadaas*); Aker Sykehus (Dr T. B. Harbitz, Dr I. Liavaag*); Diakonissehuset Sykehus Louisenberg (Dr J. Hognestad); Diakonhjemmmets Sykehus (Dr Ø. Havig); Hamar Sykehus (Dr O. Leidal); Kongsvinger Sykehus (Dr R. Uggerud); Tynset Sykehus (Dr B. Nordbye), Gjøvik Fylkessykehus (Dr S. Asen); Ringerike Sykehus (Dr P. Holme); Vestfold Sentralsykehus (Dr O Holter); Horten Sykehus (Dr N. Kollevold); Sandefjord Sykehus (Dr O. Ruistuen); Larvik Sykehus (Dr B. Sundal); Telemark Sentralsykehus (Dr G. Haarberg); Notodden Sykehus (Dr A. Skauby); Aust-Agder Sentralsykehus (Dr E. Stenehjem); Vest-Agder Sentralsykehus (Dr B. I. Haug); Mandal Sykehus (Dr P. E. Hansen); Farsund Sykehus (Dr A. Nysted); Sentralsykehuset i Rogaland (Dr R. Hoel); Fylkessjukehuset i Haugesund (Dr J. Heggebø); Haukeland Sykehus (Dr B. Arnesjø*, Dr C. W. Janssen*); Diakonissehjemmets Sykehus, Haraldsplass (Dr F. P. Gullaksen); Hospitalet Betanien (Dr J. Thunold); Fylkessjukehuset på Stord (Dr O. Stray); Fylkessjukehuset i Odda (Dr K. Svendby); Fylkessjukehuset på Voss (Dr A. Reisaeter); Fylkessjukehuset i Florø (Dr O. Husebø); Lærdal Sjukehus (Dr Krogh-Sørensen); Fylkessjukehuset i Ålesund (Dr N. Andersson), Fylkessjukehuset i Volda (Dr Y. Norderval); Fylkessjukehuset i Molde (Dr T. Hasselgård); Fylkessykehuset i Kristiansund N. (Dr T. Tennøe); Regionsykehuset i Trondheim (Dr H. Fjøsne); Orkdal Sanitetsforenings Sykehus (Dr H. G. Erichsen); Innherred Sykehus (Dr T. Bjerkeset*); Sandnessjøen Sykehus (Dr Ø. Ylvisaker); Gravdal Sykehus (Dr O. Høstmælingen); Narvik Sykehus (Dr T. Teigan); Regionsykehuset i Tromsø (Dr K. Nordstrand, Dr J. A. Johnson*); Harstad Sykehus (Dr G. Thorsen); Hammerfest Sykehus (Dr E. Andersen); Kirkenes Sykehus (Dr O. Rojahn); The Cancer Registry of Norway (Dr E Glattre*).

---

* Indicates a member of the working party

Br. J. Surg. 1988, Vol. 75, July,
713–716

Role of adhesive wraps in the pathogenesis of complicated amoebic colitis

F. M. Luvuno

Department of Surgery, University of Natal Medical School and King Edward VIII Hospital, Durban, South Africa

Correspondence to:
Mr F. M. Luvuno, Department of Surgery, University of Natal Medical School, P.O. Box 17039, Congella 4013, South Africa

Ischaemic foci within the abdomen attract omental and peritoneal adhesions with neovascularization. Previously it has been shown that transmural amoebic colitis is an ischaemic process. An intra-operative evaluation of the peritoneal barriers in response to necrosis was undertaken during laparotomy in 82 patients with clinical transmural amoebic colitis. At operation the ischaemic colon was covered by adhesive wraps in all patients; peritonitis subsequently was absent in 23 patients (28 per cent), serous in 43 patients (52 per cent), purulent in only 9 patients (11 per cent) and faeculent in another 7 patients (9 per cent). The author regards wrapping as mechanically protective. Wrapping is also a source of neovascularization which was demonstrated on 10 angiograms of resected specimens with transmural disease. This is further supported by clinical finding of subsequent necrosis of colons in three patients whose wraps were disturbed at laparotomy without resection of the colons. Therefore, for both mechanical and vascular reasons, these wraps should not be disturbed.

Keywords: Ischaemic amoebic colitis, revascularization, omental adhesion

Transmural amoebic colitis is defined as progressive ischaemic necrosis of the entire thickness of the colonic wall including the serosa[1]. At laparotomy the most striking finding is marked adhesion formation between the ischaemic colon and omentum and other adjacent structures. It would appear that as the colon dies it provokes a response which leads to adhesive wrapping. This is in keeping with other studies which have shown that ischaemic intestine results in adhesions 'similar to vascular grafts into the ischaemic area'[2]. This study examines the role and efficacy of adhesive wraps, by prospective evaluation of the intra-abdominal findings at laparotomy for suspected transmural disease in patients with amoebic colitis.

Patients and methods

During the period June 1978 to July 1985, laparotomy was performed for suspected transmural disease in 82 patients suffering from severe amoebic colitis. Resected specimens from 10 patients were also examined: (1) macroscopically, to assess the relationship of the adhesive wraps to transmural disease, and (2) by angiography, to determine the pattern of vascular distribution of the adhesive wraps. At laparotomy the abdominal cavity was assessed for the type of peritonitis and the distribution and efficacy of adhesive wraps. Lastly, the effect of intra-operative dismantling of the wraps during the assessment of the extent of transmural disease was noted in three referred patients.

Type of peritonitis at laparotomy

Peritonitis was defined as absent, serous, purulent, or faecal depending on the condition of the peritoneal fluid on entering the abdominal cavity, before any manipulation of the abdominal contents.

Distribution of the adhesive wraps at laparotomy

The distribution of adhesive wraps was assessed before manipulation of the abdominal contents. Adhesions of omentum, bowel, abdominal wall or any other organ sealing off transmural disease were noted.

Angiographic examination

Angiograms of the wraps were performed in 10 resected specimens obtained from patients with transmural amoebic colitis. The arteries related to the adhesions or mass were cannulated and radiographs were taken after gentle injection of contrast medium (Conray 280, Maybaker, South Africa). The presence of abnormal vascular pattern and bridging vessels were noted. The angiograms of 10 normal colons obtained at necropsy, on patients who died of diseases other than those of the gastrointestinal and the vascular systems, were available for comparison.

Macroscopic appearances of adhesive wraps

Ten specimens from patients in whom the surgeon had decided to undertake resection were examined macroscopically. The bowel was opened longitudinally along the antimesenteric border over the wraps and the cut surface inspected to assess the relationship of adhesive wraps to transmural disease. Cut sections were photographed to provide a permanent record.

Intra-operative dismantling of the adhesive wraps

Three patients with transmural amoebic colitis were operated under the care of a different team of surgeons. The adhesive wraps of all three patients had been dismantled at the initial laparotomy to assess the extent of transmural disease. Two patients failed to improve and were re-explored; the third died and was subjected to a post-mortem examination.

Results

Initial operative findings

The initial operative findings in 82 patients are shown in *Table 1*. Serous peritoneal exudate or adhesive wraps with minimal amounts of peritoneal fluid were the most commonly encountered findings on entering the abdomen. Faecal peritonitis, usually localized around a free perforation of an area not covered by a wrap, occurred in seven patients. Purulent peritonitis without an obvious uncovered perforation was present in areas not covered by the wraps or covered by poor thick creamy pus of pyogenic sepsis was not seen. Transmural disease was walled off by adhesive wraps of varying efficiency in all patients (*Table 1*). In seven patients free perforations were present in areas not covered by the wraps or covered by poor

0007-1323/88/070713-04$3.00 © 1988 Butterworth & Co (Publishers) Ltd

quality wraps which disintegrated easily during laparotomy; these were usually adhesions to the abdominal wall and small intestine that dismantled during access to the abdominal cavity and exposure of the colon respectively. The most efficient and firm adhesive wraps were those of the omentum and of the mobile parts of the colon, usually the transverse colon but occasionally the sigmoid. These were in danger of being dismantled during assessment of the extent of transmural disease before resection because the ischaemic areas were buried beneath the wraps. The omentum was always a pointer to what appeared to be the most severely diseased part of the colon. In extensive disease the right colon and transverse colon were often covered by firmly adherent omentum. The left colon including the sigmoid was often covered by small bowel adhesions which separated readily on minimal manipulation thus exposing the underlying perforation or necrosis.

Table 1 *Initial laparotomy findings in 82 patients operated for suspected amoebic colitis (1978–85)*

Laparotomy findings	Cases (no.)	(Percentage)
Peritonitis fluid		
Faeculent*	7	(9)
Purulent	9	(11)
Serous	43	(52)
None (adhesive wraps only)	23	(28)
Total	82	
Adhesive wraps		
Covering all diseased colon	79	(91)
Leaving gaps uncovered*	7	(9)
Total	82	

* Patients with faeculent fluid had incomplete adhesive wraps

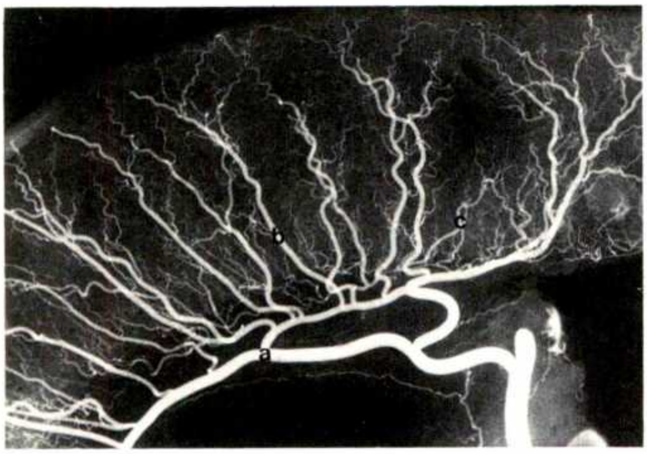


Figure 1 *Normal specimen angiography of the colon demonstrating marginal artery* (**a**)*, which gives rise to vas longum* (**b**) *and vas brevis* (**c**)*. These vessels run at right angles to the long axis of the colon*

Angiography

A normal pattern of a colon specimen angiogram is shown in *Figure 1*. The colonic marginal artery gives off vasa brevia and vasa longa, and these vessels supply the colon in a recognizably ordered pattern. Injection of contrast into vessels of the wrappings, whether omental or peritoneal, produced evidence of neovascularization of varying maturity in all 10 resected specimens studied. Where a transmural lesion appeared clinically to be an early lesion (seven specimens), adhesive wraps produced two types of angiographic abnormality, namely abnormal pattern of vasculature and fine bridging vessels running between the colon and the omentum (*Figure 2*). When the lesions were more advanced (three specimens), neovascularization was demonstrated by large omental, and leashes of peritoneal vessels (*Figure 3*). In any one patient, the vascular pattern could be either early or advanced, or both, depending on different ages of transmural lesions. Early neovascularization was represented by fan-shaped placenta-like vessels (see (f) on *Figure 2*), whereas late or advanced neovascularization was by well-formed vessels (see *Figure 3B*).

Macroscopic examination of adhesive wraps

The distribution of adhesive wraps in amoebic colitis could be correlated with the extent of transmural lesions. Ischaemic vascular lesions were buried deep to the wraps. The adhesive wrappings, especially of omentum, were plastered firmly to the ischaemic colon lesions by exudate. Whenever a wrap was

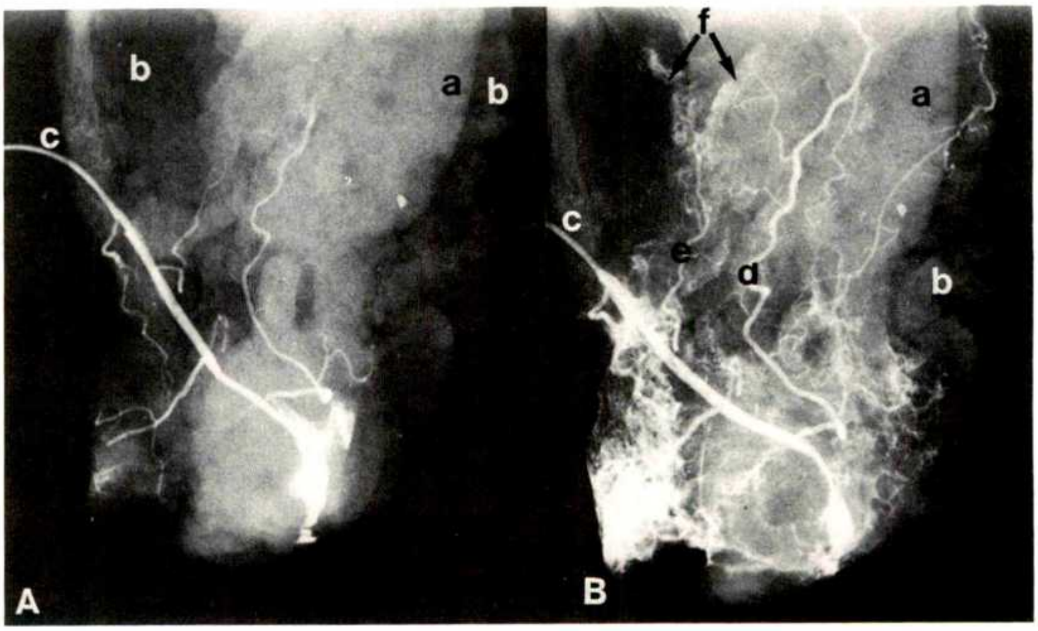


Figure 2 **A** *early and* **B** *late phases of a specimen angiography of a resected colon* (**a**)*, which is opaque and clearly demarcated from translucent omental wraps* (**b**)*. Injection of contrast into an omentum vessel* (**c**) *demonstrates vessels running longitudinal to the colon* (**d**) *and bridging vessels* (**e**) *fanning out to omentum and colon* (**f**)*. Many such fan-shape areas are visible on the late phase angiograph and the colon is even more opaque*

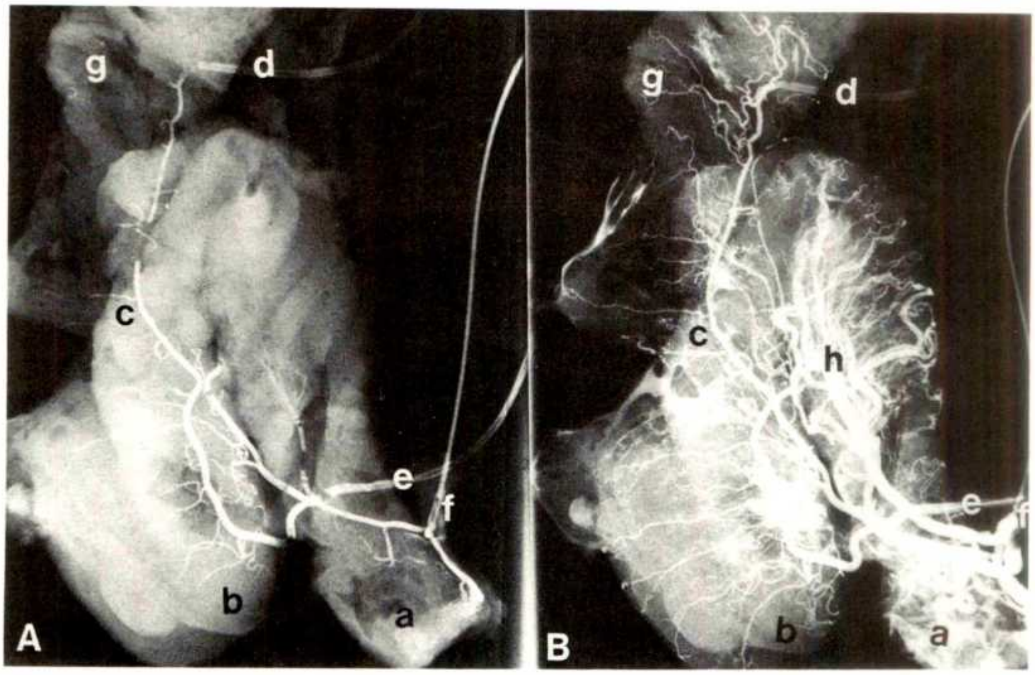


Figure 3 **A** *early and* **B** *late phases of a specimen angiography of a resected right colon with transmural disease. The proximal transverse colon* (**a**) *has 'migrated' to patch the caecum* (**b**) *and ascending colon* (**c**). *Injection of contrast into omental vessel* (**d**) *or vessels on the antimesenteric border of the proximal transverse colon* (**e** *and* **f**) *demonstrates well-formed vascular connection between omentum* (**g**), *right colon* (**c**) *and transverse colon* (**a**), *and further demonstrates a leash of vessels* (**h**) *between contiguous borders of the ascending colon* (**c**) *and transverse colon* (**a**)

dismantled at laparotomy, profuse punctuate bleeding was produced on both surfaces, suggesting an attempt at revascularization and grafting of the ischaemic colon.

Consequences of dismantling the wraps

Three patients who underwent laparotomy for suspected amoebic colitis, in whom adhesive wraps were dismantled and the bowel looked clinically intact, deteriorated postoperatively. Two required relaparotomy. *Figure 4* shows the pre-operative angiogram obtained before relaparotomy. This patient had undergone laparotomy earlier for suspected amoebic colitis perforation. At the initial laparotomy a free perforation was not found; adhesions of omentum to the colon were dismantled but no clinically obvious necrosis was noted. Despite adequate intensive care, the patient deteriorated and a mesenteric angiogram was performed after 7 days from the first operation and showed avascular colon (*Figure 4*). On this evidence the patient underwent colectomy where the colon was found to be frankly necrotic. Post-mortem examination of the third referred patient revealed more advanced necrosis of the remaining colon after a previous extended left hemicolectomy.

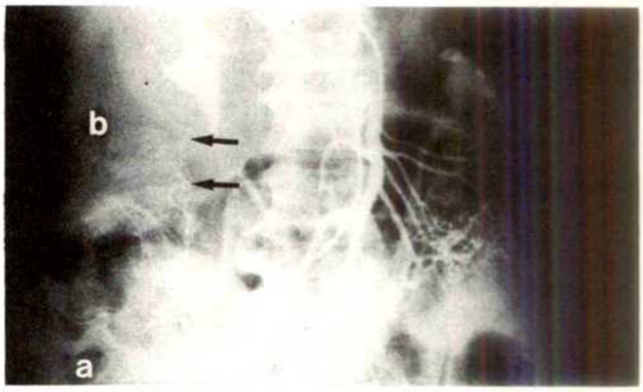


Figure 4 In vivo *selective superior mesenteric angiogram obtained before relaparotomy in a patient with fulminating amoebic colitis, demonstrating avascular caecum* (**a**) *and right colon* (**b**). *A feeble marginal artery (arrows) runs parallel to the avascular right colon. This angiogram enabled a reoperative diagnosis of transmural necrosis to be made*

Discussion

Previous discussions on the pathogenesis of the lesions of complicated amoebic colitis analysed in detail the mucosal lesions[3-5] and emphasized the destructive aspect of the disease. Rogers (1913) focused essentially on the destructive aspect of severe amoebic colitis, noting that in the post-mortem studies the gangrenous colon was as friable as 'damp blotting paper'[4]. From this concept there evolved the idea of two types of perforation: free colonic perforation leading to acute peritonitis for which surgery was advocated, and 'seepage' peritonitis with no obvious perforation, where surgery was contra-indicated[6]. Although adhesive wraps have long been described[7], their clinical significance in the evolution of the disease process was not adequately appreciated while this false classification of perforation persisted.

Recently Stein *et al.* (1979) advocated subtotal colectomy in fulminating amoebic colitis if 'substantial clinical improvement does not occur rapidly with intensive medical therapy'[8]. Both those who regard any surgery as unwarranted and those who regard radical surgery as treatment of choice, completely disregard the role of adhesive wraps and recognize only the destructive element of fulminating amoebic colitis. Failure to recognize the protective mechanism of adhesive wrap in the pathogenesis of complicated amoebic colitis may precipitate unnecessary radical surgery.

Evidence from this study suggests that the destructive ischaemic transmural necrosis of the colon in amoebic colitis is associated with protective adhesive wraps in most cases. Very early in the development of transmural disease, adhesive wraps form on the peritoneal surface of the colon to protect sites of possible perforation, as indicated by instances where the wraps were removed and the colon, although appearing viable at the time, subsequently necrosed. Areas of potential ischaemic necrosis are covered by omentum, small and large bowel, anterior abdominal wall, or appendices epiploicae. Adhesive infolding of the colonic haustra bury the infarcted areas. Uninvolved segments of colon, usually the transverse colon or sigmoid, migrate to patch up areas threatened by ischaemic necrosis.

The most characteristic adhesions are those of the omentum which becomes oedematous, thickened, vascular and firmly adherent to areas of potential infarction which it revascularizes. Ellis (1971) showed that ischaemia causes adhesion formation, and that these adhesions are similar to vascular grafts into the ischaemic tissue[2]. This finding is so characteristic that absence of omental wrapping should raise doubts about the diagnosis.

The adhesive wraps mechanically protect the peritoneal cavity from faecal contamination. The small number of patients with faecal peritonitis (9 per cent), the large number of patients with serous peritonitis (52 per cent) or adhesions only (28 per cent) in this series all bear testimony to the mechanical protective role of the adhesive wraps in amoebic colitis. It is also important to note that free perforations were found only in unprotected areas. The bacterial contamination by intestinal organisms from the lumen of the colon is probably a significant factor in outcome, and removal of these organisms mechanically may improve outcome. To test this hypothesis a study is under way in which the colon is emptied by perileal on-table antegrade lavage with removal of gut content through the anus[9]. The initial results are encouraging.

Acknowledgement

I wish to express my sincere gratitude toward Professor Hugh A. Dudley for his continued interest in, and constructive criticism of, my work.

References

1. Luvuno FM, Mtshali Z, Baker LW. Vascular occlusion in the pathogenesis of complicated amoebic colitis: evidence for an hypothesis. *Br J Surg* 1985; **72**: 123–7.
2. Ellis H. The cause and prevention of post-operative intraperitoneal adhesions. *Surg Gynecol Obstet* 1971; **133**: 497–511.
3. Councilman WT, Lafleur HA. Amoebic dysentery. *Johns Hopkins Hosp Rep* 1891; **2**: 395–548.
4. Rogers L. *Dysenteries: Their Differentiation and Treatment*. London: Oxford University Press, 1913.
5. Brandt H, Tamayo RP. Pathology of human amoebiasis. *Human Pathol* 1970; **1**: 351–85.
6. Wilmot AJ. *Clinical Amoebiasis*. Oxford: Blackwell, 1962.
7. Woolley PG, Musgrave WE. The pathology of intestinal amoebiasis. *JAMA* 1905; **65**: 1366–78.
8. Stein D, Bank S, Louw JH. Fulminating amoebic colitis. *Surgery* 1979; **85**: 249–352.
9. Dudley HAF, Radcliffe AG, McGeehan D. Intraoperative irrigation of the colon to permit primary anastomosis. *Br J Surg* 1980; **67**: 80–1.

Paper accepted 17 January 1988

Br. J. Surg. 1988, Vol. 75, July, 717

Cure of a bleeding duodenal varix by sclerotherapy

Ph. Gertsch and L. H. Blumgart

Clinic for Visceral and Transplantation Surgery, University of Bern, Switzerland

Correspondence to: Dr Ph. Gertsch, Klinik für Viszeral- und Transplantationschirurgie, Inselspital, 3010 Bern, Switzerland

The high mortality of bleeding duodenal varices has been emphasized previously[1-4]. Only two cases of endoscopic sclerotherapy have been published to date. We report a third case which demonstrates the potential of sclerotherapy in this dangerous situation.

Case report

A 40-year-old woman was hospitalized for a second episode of massive gastrointestinal bleeding. She had a history of chronic alcoholism, and bleeding oesophageal varices had been treated successfully by endoscopic sclerotherapy 2 years earlier.

On admission, the patient had ascites, jaundice and evidence of encephalopathy. Laboratory findings were: Quick 25 per cent, albumin 24 g/l, total bilirubin level 3 mg/dl, and platelets 60 000/mm^3. Endoscopic examination showed small and non-bleeding oesophageal varices; there was some blood in the stomach and a prominent ulcerated varix was identified in the duodenum (*Figure 1*). Endoscopic sclerotherapy was performed by injecting 25 cm^3 of polidocanol 1 per cent into the varix. Although no further bleeding occurred during the following days, hepatic coma complicated the situation. Ten days later 10 cm^3 of absolute alcohol was injected into the duodenal varix during massive recurrent bleeding.

The patient recovered slowly without further bleeding and left hospital 1 month later. Endoscopy was repeated at 6-monthly intervals. Her general condition improved after complete alcohol abstinence, with change from Child's category C to A. Small recurrent oesophageal varices were sclerosed on two occasions. The duodenal varix had disappeared and no recurrence was observed after a follow-up of 3 years (*Figure 1*).

Discussion

Endoscopic sclerotherapy for bleeding duodenal varices has been reported in two cases, one after thrombosis of a portocaval shunt in a patient with cirrhosis of unknown aetiology, and another in an alcoholic cirrhotic patient[6,7]. Recurrent bleeding was not observed after an 18-month follow-up in the first case.

Our case demonstrates that endoscopic sclerotherapy can be efficient even in the presence of acute bleeding and that it can provide definitive cure. It is important to be aware of the possibilities of this form of treatment as the mortality rate after surgery varies between 30 and 40 per cent, and bleeding recurs after non-shunting operations in from 40 to 57 per cent of cases[5].

The question arises of whether prophylactic treatment should be considered for prominent duodenal varices since haemorrhage following rupture is massive and often fatal[1-4]. Bleeding varices are more difficult to detect and to treat by endoscopic means in the duodenum than in the oesophagus. Immediate haemostasis is not possible as it is by balloon tamponade in the oesophagus or gastric fundus. Prophylatic injection, therefore, might be rewarding.

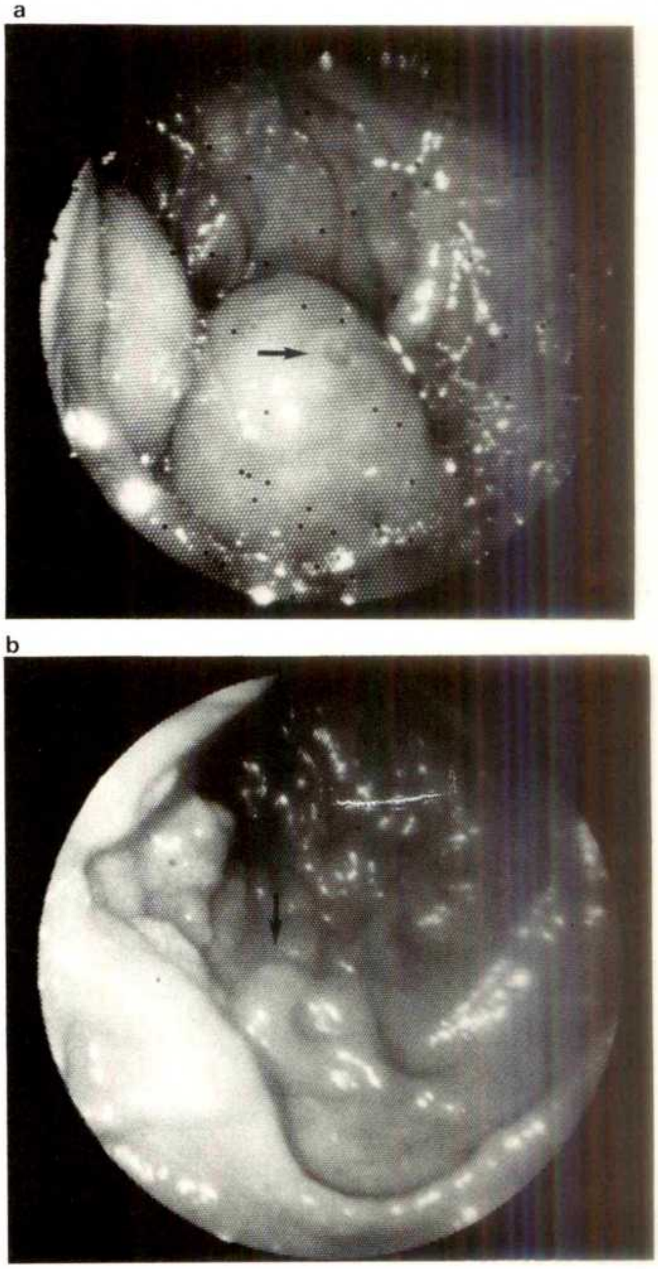


Figure 1 *Endoscopic view of the second part of the duodenum.* **a** *Ulcerated (arrow) duodenal varix before endoscopic sclerotherapy;* **b** *duodenoscopy 3 years after sclerotherapy (a small nodule is the only remnant of the varix (arrow)*

References

1. Wilson SE, Stone RT, Christie JP, Passaro E. Massive lower gastrointestinal bleeding from intestinal varices. *Arch Surg* 1979; **114**: 1158–61.
2. Kunert H, Ottenjann R. Endoscopy in bleeding duodenal varices. *Endoscopy* 1976; **8**: 99–101.
3. Perchik L, Max TC. Massive haemorrhage from varices of the duodenal loop in a cirrhotic patient. *Radiology* 1963; **80**: 641–4.
4. Gertsch P, Mosimann R. Varices gastriques ou duodenales isolees. *Schweiz Rundsch Med Prax* 1984; **73**: 1147–8.
5. Khouqeer F, Morrow C, Jordan P. Duodenal varices as a cause of massive gastrointestinal bleeding. *Surgery* 1987; **102**: 548–52.
6. Sauerbruch T, Weinzierl M, Dietrich HP, Antes G, Eisenburg J, Baumgartner G. Sclerotherapy for a bleeding duodenal varix. *Endoscopy* 1982; **14**: 187–9.
7. Kirkpatrick JR, Shoenut JP, Micflikier AB. Successful injection sclerotherapy for bleeding duodenal varix in intrahepatic portal obstruction. *Gastrointest Endosc* 1985; **31**: 259–60.

Paper accepted 1 February 1988

0007–1323/88/070717–01$3.00

Br. J. Surg. 1988, Vol. 75, July 718

Treatment of pancreatic fistula with the somatostatin analogue SMS 201-995

B. Ahrén, K.-G. Tranberg and S. Bengmark

Department of Surgery, Lund University, S-221 85 Lund, Sweden

Correspondence to: Dr B. Ahrén

Somatostatin inhibits exocrine pancreatic secretion[1,2] and has been used for treatment of pancreatic fistula[3–5]. The short $t_{\frac{1}{2}}$, <3 min in man[6], and the risk of a rebound effect when treatment is interrupted[7], require the peptide to be continuously infused intravenously. This may be circumvented by using the stable somatostatin analogue SMS 201-995 (Sandostatin), a fragment of somatostatin with full biological effect but with resistance to the degrading enzymes[8]. In man, this analogue, which can be administered subcutaneously, has been demonstrated to exert the biological actions of somatostatin[9], including the inhibition of exocrine pancreatic secretion[9,10]. We describe here the use of SMS 201-995 for treating a patient with a postoperative pancreatic fistula.

Case report

The patient was a 74-year-old woman who observed tanned stools on 12 August, 1986. A colon enema showed a polypoid tumour with a base of 4 cm situated at the lienal flexure. At operation on 25 August, the colon tumour was resected together with 20 cm of colon. Unexpectedly, a small, hard, cystic mass was found in the body of the pancreas. The appearance suggested a cystadenoma and the tumour was excised with a small wedge resection. Pathological examination showed that the pancreatic tumour was a cystadenoma. Postoperatively, the patient developed a slight hyperamylasaemia which peaked at 23 μkat/l (upper reference limit 5 μkat/l) on the second postoperative day. Gastrointestinal recovery was uneventful and oral intake was started on the third postoperative day. However, the patient developed a pancreatic fistula (*Figure 1*) with amylase levels ranging from 965 (5 September) to 1530 (27 November) μkat/l. The pancreatic fistula fluid, which was collected in a colostomy bag, was the only postoperative complaint and the patient was discharged 3 weeks after the operation. She continued to do quite well but had three episodes of blocked drainage of the fistula (with pancreatic pseudocyst formation) giving upper abdominal pain until drainage was re-established. Treatment with SMS 201-995 (Sandostatin; Sandoz Ltd., Basle, Switzerland), was started on 28 November at a dose of 50 μg given twice daily subcutaneously. As is seen in *Figure 1*, the amount of fluid dropped on the first day of treatment and stopped completely the next day. Treatment with Sandostatin continued until 4 December. At that time, the fistula opening had closed. No side-effects were observed during the treatment. Regular measurements of blood glucose levels showed normal values, as did determinations of fasting plasma levels of insulin, C-peptide and glucagon.

The patient has remained free of symptoms after treatment with SMS 201-995. However, a computer tomography performed 3 weeks after treatment showed two small cysts in the head of pancreas. A repeat tomography 4 months later demonstrated one cyst with a diameter of 6 cm. The cyst has been evacuated twice under ultrasonographic control and is now (September 1987) barely demonstrable.

Discussion

Somatostatin inhibits the secretion of secretin and cholecystokinin[11,12] and binds to pancreatic acinar cells reducing their synthesis of cyclic AMP[13]. These findings suggest that somatostatin inhibits pancreatic exocrine secretion both directly and indirectly and explain the beneficial effect of somatostatin in the treatment of pancreatic fistulae[3–5]. The somatostatin analogue SMS 201-995 (Sandostatin) has been demonstrated to inhibit meal- and cholecystokinin-induced pancreatic enzyme secretion in man[9,10]. It was anticipated that this analogue would be effective in the treatment of pancreatic fistulae. The rapid closure of the fistula in our patient supports such an assumption: the secretion through the fistula stopped within 2 days of treatment and the fistula opening closed within a week.

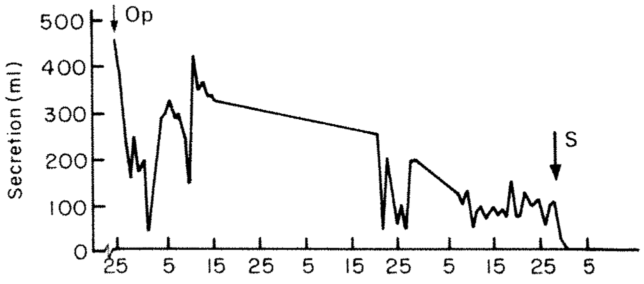


Figure 1 *Daily fluid secretion (ml) from the postoperative pancreatic fistula. The operation was performed on August 25 and treatment with Sandostatin was given between November 28 and December 4 ↓, day of operation; ↓■, Sandostatin given*

Somatostatin has been used for treating a variety of surgical conditions, such as upper gastrointestinal bleeding, gut and pancreatic endocrine tumours, secretory diarrhoea and gastro-enteropancreatic fistulae[3–5,7,14]. It is likely that the somatostatin analogue Sandostatin can be used instead. We suggest from this case report that Sandostatin might be used for treating pancreatic fistulae.

References

1. Boden G, Sivitz MC, Owen OE, Essa-Koumav N, Landon JH. Somatostatin suppresses secretin and pancreatic exocrine secretion. *Science* 1975; **190**: 163–5.
2. Dollinger HC, Raptis S, Pfeiffer EF. Effects of somatostatin on exocrine and endocrine pancreatic function stimulated by intestinal hormones in man. *Horm Metab Res* 1976; **8**: 74–8.
3. DiCostanzo J, Cano N, Martin J. Somatostatin in persistent gastrointestinal fistula treated by total parenteral nutrition. *Lancet* 1982; **ii**: 338–9.
4. Hild P, Dobroschke J, Henneking K. Behandlung enterokutaner Fisteln mit Somatostatin. *Klinikarzt* 1986; **15**: 24–9.
5. Pederzoli P, Bassi C, Falconi M, Albrigo R, Vantini I, Micciolo R. Conservative treatment of external pancreatic fistulas with parenteral nutrition alone or in combination with continuous intravenous infusion of somatostatin, glucagon or calcitonin. *Surg Gynecol Obstet* 1986; **163**: 428–32.
6. Sheppard MC, Shapiro B, Pimstone BL, Kronheim S, Berelowitz M, Gregory M. Metabolic clearance and plasma half life disappearance time of exogenous somatostatin in man. *J Clin Endocrinol Metab* 1979; **48**: 50–3.
7. Reasbeck PG. Somatostatin treatment of gastrointestinal fistulas: Evidence for a rebound effect on withdrawal. *Aust N Z J Surg* 1984; **54**: 465–7.
8. Pless J, Bauer W, Briner U *et al.* Chemistry and pharmacology of SMS 201-995, a long-acting octapeptide analogue of somatostatin. *Scand J Gastroenterol* 1986; **21**(Suppl 119): 54–64.
9. Lembcke B, Creutzfeldt W, Schleser S, Ebert R, Shaw C, Koop I. Effect of the somatostatin analogue sandostatin (SMS 201-995) on gastrointestinal, pancreatic and biliary function and hormone release in normal men. *Digestion* 1987; **36**: 108–24.
10. Köhler E, Beglinger C, Dettwiler S, Whitehouse I, Gyr K. Effect of a new somatostatin analogue on pancreatic function in healthy volunteers. *Pancreas* 1986; **1**: 154–9.
11. Raptis S, Schlegel W, Lehmann E, Dollinger HC, Zoupas C. Effects of somatostatin on the exocrine pancreas and the release of duodenal hormones. *Metabolism* 1978; **27**: 1321–8.
12. McIntosh CHS. Gastrointestinal somatostatin: distribution, secretion and physiological significance. *Life Sci* 1985; **37**: 2043–58.
13. Taparel D, Susini C, Esteve JP *et al.* Somatostatin analogs: correlation of receptor affinity with inhibition of cyclic AMP formation in pancreatic acinar cells. *Peptides* 1985; **6**: 109–13.
14. Mulvihill S, Pappas TN, Passaro E, Debas HT. The use of somatostatin and its analogs in the treatment of surgical disorders. *Surgery* 1986; **100**: 467–73.

Paper accepted 18 December 1987

Surgical workshop

Br. J. Surg. 1988, Vol. 75, July, 719

Limited conservative pancreatectomy for benign tumours: a new technical approach

P.-L. Fagniez, M. Kracht and N. Rotman

Service de Chirurgie Générale, Hôpital Henri Mondor, 51, Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

Correspondence to: Dr P. L. Fagniez

The surgical treatment of benign tumours of the pancreas until now has consisted of either formal pancreatic resection or enucleation[1,2]. None the less in tumours of the neck of the pancreas enucleation may not be possible and resection may involve either a near total pancreatectomy or a pancreaticoduodenectomy. To avoid a pancreatic resection we have designed a new procedure consisting of a resection of the neck of the gland with a complete excision of the tumour. We report here two cases of pancreatic isthmectomy performed successfully.

Patients and methods

Methods

The technique combines a limited pancreatic resection centred on the neck, with a restitution of the exocrine function by anastomozing the tail of the pancreas to a Roux-en-Y loop. The operative procedure is simple: after division of the gastrocolic ligament the pancreas is fully exposed and the superior mesenteric vein and the supraduodenal portal vein are dissected. The neck of the pancreas is then freed from its posterior attachments to the portal vein. The first section of the pancreas is performed in front of the portal vein at the right or left hand limit of the neck. The dissection then proceeds laterally and the second pancreatic section is performed just beyond the tumour. Haemostasis of the pancreatic cephalic section is assured by interrupted polyglycolic acid stitches with particular attention to the closure of the main pancreatic duct, whereas haemostasis in the distal part of the pancreas is assured in the same manner without occluding the pancreatic duct. A Roux-en-Y loop is then constructed and the pancreaticojejunal anastomosis is performed by a series of interrupted re-absorbable sutures. The anastomosis is not stented. The pancreaticojejunal anastomosis is then covered by the omentum.

Patients

Case 1. A 43-year-old woman was admitted to our hospital for repeated attacks of hypoglycaemia. Ultrasound showed a small tumour in the head of the pancreas; selective arteriography demonstrated the tumour in the cephalo-isthmic region, just to the left of the gastroduodenal artery.

Peroperative exploration confirmed the existence of an 8 mm tumour just to the right of the portal vein and to the left of the gastroduodenal artery in the posterior part of the head of the pancreas. Peroperative histological examination of a lymph node proximal to the tumour was normal. Enucleation seemed inappropriate because of the thickness of the overlying pancreatic parenchyma.

A partial pancreatectomy was performed with resection of the whole pancreas between the gastroduodenal artery to the right and the superior mesenteric vein to the left (*Figure 1*). The frozen sections confirmed the complete resection of an insulinoma, with resection margins of 0·5 cm on the right side and 2 cm on the left side of the tumour. The postoperative course was uneventful and glucose levels have been normal for 44 months.

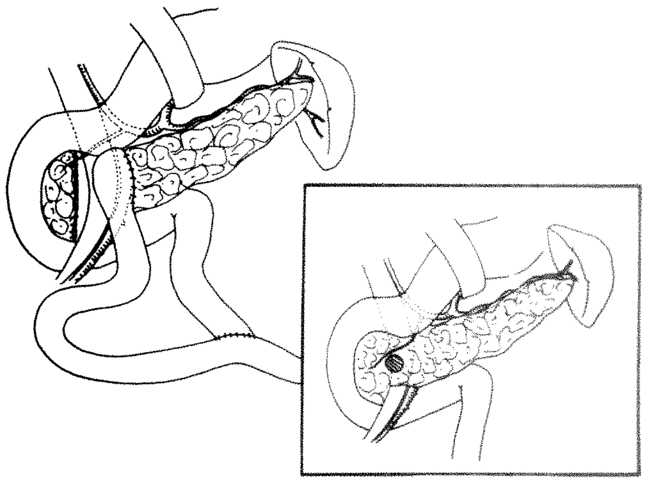


Figure 1 *Case 1: Insulinoma located just left to the gastroduodenal artery in the cephalo-isthmic part of the pancreas (right) and the operative procedure (left)*

Case 2. A 32-year-old woman was referred to our institution for a tumour of the epigastrium discovered during a routine examination. Ultrasound and CT scanning showed a cystic tumour of the neck of the pancreas, measuring 6 × 7 cm.

At laparotomy, a well-defined tumour was found in the corporeo-isthmic region of the pancreas, just anterior and to the left of the confluence of the splenic and inferior mesenteric veins. The remaining distal part of the gland was 9 cm long and was not modified by chronic inflammatory process. A partial pancreatectomy was performed and resection margins were 1 cm on all sides of the tumour. The abdomen was not drained. Histology showed the tumour to be a microcystic adenoma. The postoperative course was uneventful, and the patient left the hospital on the tenth postoperative day. The patient has been followed up for 8 months now, with normal endocrine and exocrine functions of the pancreas.

Discussion

The surgical treatment of benign pancreatic tumours has been either a formal pancreatic resection or an enucleation of the tumours[1–5]. However, resection carries a morbidity rate of up to 59 per cent and a mortality rate of up to 24 per cent in the case of pancreaticoduodenectomy or total pancreatectomy[6] and may impair the exocrine and endocrine functions of the pancreas respectively in 22 per cent and 15 per cent of the patients after pancreaticoduodenectomy[3]. Extended left pancreatectomy often implies splenectomy and may impair the glucose metabolism in up to 90 per cent of cases[1]. Enucleation may be adequate in the case of superficial tumours but may be difficult in posterior tumours inaccessible to a transparenchymal approach, as in case 1.

The choice of a surgical approach may be particularly difficult when resection of a tumour requires a pancreaticoduodenectomy to be performed as well as an extended left pancreatectomy, as in pancreatic neck tumours. In these patients, resection should be adequate to ensure a definite cure without impairing either the endocrine or exocrine function of the gland.

References

1. Stefanini P. Tumeurs langerhansiennes hypoglycémiantes. Tactique chirurgicale et résultats. *Chirurgie* 1973; **99**: 530–9.
2. Le Quesne LP, Nabarro JDN, Kurtz A, Zweig S. The management of insulin tumours of the pancreas. *Br J Surg* 1979; **66**: 373–8.
3. Warren KW, Veidenheimer MC, Pratt HS. Pancreato duodenectomy for periampullary cancer. *Surg Clin North Am* 1967; **47**: 639–45.
4. Smith R. Progress in the surgical treatment of pancreatic disease. *Am J Surg* 1973; **125**: 143–53.
5. Rustin RB, Broughan TA, Hermann RE, Grundfest-Broniatowski SF, Petras RE, Hart WR. Papillary cystic epithelial neoplasms of the pancreas. A clinical study of four cases. *Arch Surg* 1986; **121**: 1073–6.
6. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg* 1987; **206**: 358–65.

Paper accepted 29 November 1987

0007-1323/88/070719-01$3.00 © 1988 Butterworth & Co (Publishers) Ltd

Br. J. Surg. 1988, Vol. 75, July, 720

Determining safe margin of resection in low anterior resection for rectal cancer

W. O. Kirwan, J. Drumm, J. M. Hogan* and C. Keohane*

*Departments of Surgery and *Pathology, Regional Hospital, University College, Cork, Ireland*

Correspondence to: Professor W. O. Kirway, Department of Surgery, Regional Hospital, Wilton, Cork, Ireland

Precisely which cases of rectal cancer are suitable for anterior resection remains controversial. The possibility that anterior resection might achieve less satisfactory local clearance than abdominoperineal resection, as a result of its closer margins of resection, has been widely debated[1,2]. In general, initial pessimism that an unacceptably high local recurrence rate would result from anterior resection has not been sustained[3,4].

The current literature fails to provide norms with regard to the extent of distal resection required, and quoted figures vary from the classical 5 cm (reference 5) to 2 cm (reference 4). We have gradually decreased the margin of resection from 4·1 cm (reference 6) through 3·6 cm (reference 7) to a mean margin of resection of 2·5 cm in the present study.

The distal line of resection is defined precisely by the distal 'doughnut' removed from the instrument after stapled anastomosis. The objective of this prospective study was to perform detailed histopathological examination of the distal 'doughnut' in a series of 20 low anterior resections. We wished to determine whether, in any of our cases, tumour clearance was impaired by the limited longitudinal clearance achieved by anterior resection.

Patients and methods

Twenty consecutive low anterior resections were included in the study. Two tumours were Dukes' A, nine Dukes' B, six Dukes' C, and three patients had liver metastases. Nineteen tumours were moderately differentiated. One was poorly differentiated. Four tumours were situated between 0 and 5 cm, thirteen between 5 and 10 cm and three > 10 cm from the anal margin. The mean distance from anal margin was 7·9 cm.

The mean distal margin of resection (excluding the 'doughnut') on the fixed specimen was 2·5 cm. In ten patients the distal margin of resection was < 2 cm and in six it was ⩽ 1 cm. All anastomoses were performed with the EEA stapler (Auto Suture Company, UK) inserted from below. The distal purse string was inserted by hand in each case. The mesorectum was excised in all patients[3]. After fixation, the distal 'doughnut' was divided into tissue blocks which were processed in the usual way. Sections, 5 μm thick cut at 100-μm intervals through all tissue blocks, were stained with haematoxylin and eosin and examined under light microscopy by the same consultant histopathologist for evidence of tumour. The mean number of blocks obtained from each 'doughnut' was 15 and the total number of sections examined was 7626 with a mean number of 381 per 'doughnut'. All 20 'doughnut' specimens contained the full thickness of bowel wall, including venous and lymphatic channels.

All 7626 slides were examined without knowledge of the findings in the main specimen of excised rectum.

Results

In 19 of the 20 patients, which involved examining a total of 7233 sections through the distal 'doughnut', no tumour tissue was encountered.

In one patient, tumour cells were present in one of a total of sixteen blocks. This block was sectioned at 27 levels, and in 5 sections carcinoma was identified in lymphatics. In this patient a total of 393 sections were examined and 5 were positive for carcinoma. This tumour was Dukes' C with involvement of the highest node and distal submucosal spread on the pathology specimen, for a distance of 1·5 cm. Submucosal spread was not observed in the other 19 tumours.

Discussion

Much pelvic recurrence is due to extensive extra-mural ramification of the cancer. Such ramification is apparent to the surgeon and pelvic recurrence can often by predicted. In this situation the tumour should be regarded as residual cancer rather than recurrent cancer. It is wrong to attribute such pelvic recurrence to the type of operation performed.

Anastomotic recurrence appears as tumour at the anastomosis site and is due to inadequate longitudinal resection. This is the essence of the current debate. Classical margins of resection have been 5 cm (reference 5) but rigid adherence to this rule will result in the unnecessary sacrifice of many sphincters[4].

In the present series, the measured margin of resection was < 2 cm in 50 per cent of cases and ⩽ 1 cm in 30 per cent. In 19 out of 20 cases (95 per cent) there was no evidence of tumour in the 'doughnut'. In one patient the distal 'doughnut' contained cancer. This tumour was in perirectal lymphatics and represents lymphatic rather than contiguous spread. Submucosal spread occurs in approximately 10 per cent of cases[4] and indicates a poor prognosis, regardless of type of operation. Eighteen months postoperatively, no local recurrence has appeared in our cases.

We conclude that the margin of resection practised in this study is justified by the pathology findings and provides further evidence that the classical margins of resection are not necessary in low anterior resection for cancer.

Acknowledgements

This work was supported by a grant from the Irish Cancer Society.

References

1. Hurst PA, Prout WG, Kelly JM, Bannister JJ, Walker RT. Local recurrence after low anterior resection using the staple gun. *Br J Surg* 1982; **69**: 275–6.
2. Pollett WG, Nicholls RM. The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. *Ann Surg* 1983; **198**: 159–63.
3. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery. *Br J Surg* 1982; **69**: 613–16.
4. Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: A study of distal intramural spread and of patients survival. *Br J Surg* 1983; **70**: 150–4.
5. Goligher JC. *Surgery of the Anus, Rectum and Colon.* 3rd ed. London: Baillière Tindall, 1975.
6. Kirwan WO, Turnbull RB, Fazio VW, Weakley FL. Pull through operation with delayed anastomosis for rectal cancer. *Br J Surg* 1978; **65**: 695–8.
7. Kirwan WO. Integrity of low colorectal EEA-stapled anastomosis. *Br J Surg* 1981; **68**: 539–40.
8. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **i**: 996–9.

Paper accepted 8 August 1987

0007-1323/88/070720-01$3.00

Br. J. Surg. 1988, Vol. 75, July, 721

True aneurysms of the pancreaticoduodenal artery: a rare cause of retroperitoneal bleeding and delayed diagnosis

D. J. Small, P. W. J. Houghton and N. J. McC. Mortensen*

University Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Correspondence to: Mr P. W. J. Houghton

Visceral artery aneurysms are an uncommon cause of intra-abdominal bleeding[1] and their diagnosis and management may present problems to the clinician. Two cases of rupture of true pancreaticoduodenal artery aneurysms are described in which there was no history of trauma or pancreatitis.

Case reports

Case 1

A previously fit 53-year-old man was admitted with a 6-h history of severe epigastric pain and vomiting. On examination his pulse rate was 108 beats/min, and his blood pressure 130/80 mmHg. His abdomen was not distended but was tender with guarding in the right upper quadrant. He had a positive Murphy's sign and the bowel sounds were reduced. Investigations revealed a haemoglobin of 14·2 g/dl, a white cell count of $18{\cdot}2 \times 10^9$/l, and his urea, electrolytes and amylase were within normal limits. A plain abdominal X-ray showed two centrally situated dilated loops of small bowel. He was treated conservatively initially but subsequently deteriorated.

A laparotomy 12 h later revealed a large retroperitoneal haematoma with free blood in the peritoneal cavity. The abdominal aorta was found to be intact and it was only after Kocherization of the duodenum that the source of the haemorrhage was found to be a saccular aneurysm of the pancreaticoduodenal artery (*Figure 1*). Control of the bleeding was obtained by under-running the vessel and aneurysm with interrupted 4/0 silk sutures.

Case 2

A previously fit 58-year-old man was admitted with a 24-h history of colicky right upper quadrant pain and vomiting. On examination he was pale, pulse 90 beats/min, blood pressure 80/50 mmHg. His abdomen was tense with some tenderness in the right upper quadrant and a positive Murphy's sign. Investigations revealed a haemoglobin of 12·4 g/dl, white blood cell count of $13{\cdot}6 \times 10^9$/l and urea, electrolytes and amylase within normal limits. An abdominal X-ray was unremarkable. After resuscitation his vital signs became stable but 4 h later he deteriorated with increasing abdominal distension and signs of peritonitis. At laparotomy free peritoneal blood and a huge retroperitoneal haematoma were found. Dissection of the retroperitoneum revealed an intact abdominal aorta. After Kocherization of the duodenum the source of the bleeding was identified as an aneurysm of the inferior pancreaticoduodenal artery and control was obtained by under-running with 3/0 Prolene sutures (Ethicon Ltd., UK).

Discussion

Aneurysms of the visceral arteries are uncommon and pancreaticoduodenal artery aneurysms are rare, accounting for only 3 per cent of all visceral aneurysms[1]. They are usually false and frequently follow pancreatitis or pancreatic trauma and they often bleed into a pseudocyst or the gastrointestinal tract. The rarer true aneurysms are commonly due to arteriosclerosis and tend to bleed into the retroperitoneum or peritoneal cavity rather than the gastrointestinal tract[2]. West *et al.*[3] reported 12 cases where the commonest symptom was abdominal pain simulating gastric, biliary or pancreatic disease. The urgency of the condition only becomes apparent as bleeding slowly continues or occurs repeatedly. Once laparotomy is undertaken the abdominal aorta is found to be intact. Suspicion of the true diagnosis should be raised by the excessive amount of blood found in the right upper quadrant. Intra-operative angiography has been suggested as an aid to identification of the bleeding vessel[4] and intra-operative detection in other people's hands has been successful in only 30 per cent of cases[5]. After Kocherization of the duodenum, however, we found the ruptured vessel was usually obvious and, if not, stroking away all blood clot from the back of the duodenum and pancreas caused rebleeding. Once the diagnosis has been established oversewing of the artery is all that is required. Both of our patients made an uneventful recovery although West *et al.* found a 50 per cent mortality in their series[3].

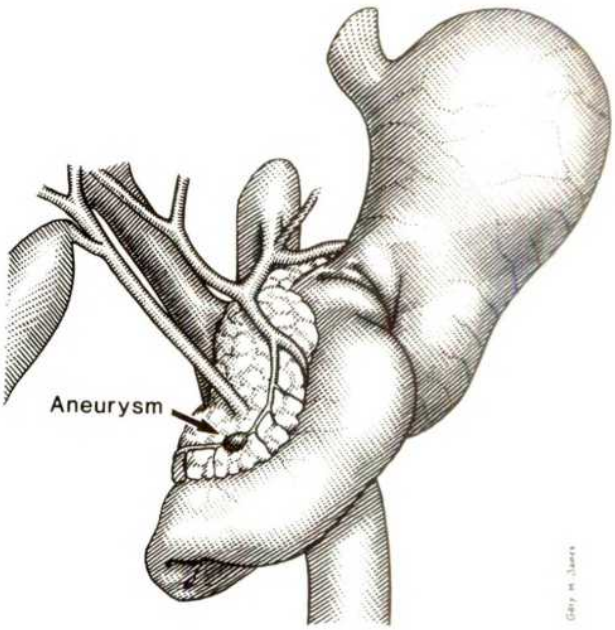


Figure 1 *Diagram showing the anatomy of the operation with the aneurysm arising from the pancreaticoduodenal artery*

References

1. Stanley JC, Whitehouse WM. Splanchnic artery aneurysms. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: WB Saunders Co, 1984: 798–13.
2. Gangahar DM, Carveth SW, Rees HE *et al.* True aneurysm of the pancreaticoduodenal artery: a case report and review of the literature. *J Vasc Surg* 1985; **2**: 741–2.
3. West JE, Bernhardt H, Bowers RF. Aneurysms of the pancreaticoduodenal artery. *Am J Surg* 1968; **115**: 835–9.
4. Spanos PK, Kloppedal EA, Murray CA. Aneurysms of the gastroduodenal and pnacreaticoduodenal arteries. *Am J Surg* 1974; **127**: 345–8.
5. Retzlaff JA, Hagedorn AB, Bartholomew LG. Abdominal exploration for gastrointestinal bleeding of obscure origin. *JAMA* 1961; **177**: 104–7.

Paper accepted 27 October 1987

0007–1323/88/070721–01$3.00

Short note

Br. J. Surg. 1988, Vol. 75, July, 722

Bowel movement and diet in patients with stomas

F. Giunchi, G. Cacciaguerra, M. L. Borlotti*, A. Pasini† and G. Giulianini*

*Department of Surgery, *Ostomy Rehabilitation Service and †Dietary Service, M. Bufalini Hospital, Cesena, Italy*

Correspondence to: Dr F. Giunchi, via Trovanelli 144, 47023 Cesena, Italy

The literature is replete with advice for patients with abdominal stomas, whether ileostomies or colostomies[1-6]. Undoubtedly diet is important in the management of the stoma[5] but equally compliance with a very strict diet is unnecessary. The aim of this survey is to decide whether the balance of diet and eating habits affect bowel movement in such a way as to make management of the stoma more difficult.

Patients and methods

A questionnaire was given to each patient followed up by our Ostomy Rehabilitation Service; each patient had to list both the type and quantity of foods eaten every day for a week and had to answer questions on the use of irritant foods (fried foods, spices, chocolate etc.) and fresh fruit and vegetables (whether normal or aromatic and irritant, onion, cabbage, peppers etc.). The questionnaire included a series of questions on the regularity and type of bowel movement.

Questionnaires were given to 165 patients but only 100 satisfactory returns were obtained: 40 from colostomates who did not irrigate; 50 from colostomates who irrigated; and 10 from ileostomates. From each questionnaire the total calorie intake and the intake of proteins, lipids and carbohydrates were calculated. The amount of roughage, the presence of irritant foods and the distribution of the meals throughout the day were recorded. The body weight and the intake of calories, proteins, carbohydrates and lipids were used to evaluate the nutritional state. All parameters were related to stoma function. Normal values for body weight and nutritional intake were taken from those published by the Italian Institute of Nutrition[1].

The 100 questionnaires reviewed were submitted by patients who had no evidence of relapse of their disease (neoplastic or inflammatory) to eliminate the impact of a deteriorating clinical state on diet and stoma function. The 10 ileostomy patients had had their operations more than 1 year before the survey, as had most of the colostomates. Thus, stoma function could be assumed to be settled in all those surveyed.

Results

Body weight was within the normal limits in 62 per cent of the subjects examined; 34 per cent were overweight and only 4 per cent were underweight. The calorie intake was fairly balanced between those taking insufficient (26 per cent), sufficient (31 per cent) and high (29 per cent) calorie diets. Most patients had a high intake of protein; this is consistent with statistics for the whole Italian population. The lipid intake was sufficient in 45 per cent of patients and insufficient in 26 per cent; also most patients (63 per cent) had a sufficient intake of carbohydrates. Stoma patients took a much lower intake of roughage than is general in the population as a whole, and patients tended to reduce their intake of 'irritant' vegetables, with 39 per cent avoiding these foods completely[6]. The distribution of the meals was 'good' in 54 per cent, and 'irregular' in 46 per cent.

In the group of 40 patients who do not carry out irrigation, 29 (72 per cent) have regular bowel movement (1 or 2 evacuations a day) and 11 have irregular bowel movement (more than 2 evacuations a day). As far as regularity is concerned, a good distribution of the meals throughout the day is important. The results from this sample show that a moderate, or even marked, use of irritant foods is not accompanied by particular problems of bowel movement.

In the group of 50 patients who carry out irrigation every 24 or 48 h, 23 have good continence and 27 have fairly good continence; the distribution of the meals throughout the day is important in those patients carrying out irrigation (48 per cent had a good distribution of meals throughout the day). The use of irritant foods is not harmful as long as the intake is moderate. The evaluation of the data concerning the use of roughage does not produce clear results: the fact that the 'very low' use of roughage predominates in the second group (63 *versus* 57 per cent), which would seem to confirm the importance of fibre for evacuation, is not supported by the fact that the 'normal' consumption of fibre is higher in the second group than in the first (7·4 *versus* 4·4 per cent). Of the 10 patients with ileostomy three usually emit solid faeces, while 7 emit soft or liquid faeces.

The only two conclusions we tentatively draw are that regular good eating habits are associated with more liquid faeces from the stoma and irritant vegetables (onions, peppers etc.) and roughage do not cause an alteration in faecal output.

Discussion

The results of our survey show the importance of correct eating habits for patients bearing abdominal stomas. In particular, a correct distribution of the meals throughout the day is important for colostomized patients, whether they carry out irrigation or not. The use of irritant foods (spices, fried foods, aromatic vegetables) which are normally excluded from the diet of these patients does not give rise to problems for the bowel movement as long as there is a 'moderate' use of them. Indeed, in some of the patients who do not irrigate even an increased use may be helpful and should be permitted. The use of vegetable roughage is insufficient in all the subjects who took part in our survey, but this does not seem to lead to particular problems with the bowel movement.

References

1. Carnovale E, Miuccio FC. Tabelle di composizione degli alimenti. Istituto Nazionale della Nutrizione Roma 1981.
2. Gazzard BG, Saunders B, Dawson M. Diets and stoma function. *Br J Surg* 1978; **65**: 642
3. Hunker EM. Nutrition therapy for the ostomy patient. In: Broadwell DC, Jackson BS, eds. *Principles of Ostomy Care*, St Louis: C.V. Mosby Company. 1982.
4. Murphy M. Dietary consideration and the use of bran. In: Brockman B, ed. *Stoma Care*. Beaconsfield, UK: Beaconsfield Publishers, 1981: 151–7.
5. Rebuffat C, Negri G, Maruotti RA *et al*. Stoma function in patients with a left colostomy: the importance of dietary management. *Journal of Enterostomal Therapy* 1983; **10**: 200.
6. Terranova O, Sandei F, Rebuffat C, Maruotti RA, Bortolozzi E. Irrigation vs natural evacuation of left colostomy: a comparative study of 340 patients. *Dis Colon Rectum* 1979; **22**: 31.

Paper accepted 1 November 1987

Correspondence

Aorto-enteric fistulae

Sir

Mr Collin's suggestion (*Br J Surg* 1988; 75: 292), that the peritoneum over an aortic graft can be confidently left to close itself, cannot go by unchallenged. Personal experience in reoperating on patients whose aortic grafts have not been covered has shown that this does not happen. In all cases the small bowel was densely adherent to the graft, and aorto-enteric fistulae occurred in a significant proportion[1].

The experimental study quoted looked at the incidence of aortoduodenal fistulation in dogs at 6 weeks, but in the clinical situation this may occur some years after the initial graft has been inserted. The paper also stresses the importance of trying to place a viable tissue barrier between the duodenum and the graft, and I am sure this should form part of basic surgical teaching.

A. R. Turnbull

Royal United Hospital
Bath
UK

1. Umpleby HC, Britton DC, Turnbull AR. Secondary arterio-enteric fistulae: a surgical challenge. *Br J Surg* 1987; 74: 256–9.

Author's reply

Sir

Mr Turnbull is incorrect in assuming that his personal experience of operating on patients with arterio-enteric fistulae proves the case for closure of the posterior peritoneum. The advocacy, in Umpleby's paper[1], of Dacron® cuffs, aneurysm sac closure, omental interposition and 'careful' reperitonealization is unreferenced and conversational A more plausible explanation for the development of the arterio-enteric fistulae is chronic sepsis since none of the ten patients had received adequate prophylactic antibiotic cover for their original aortic surgery.

J. Collin

John Radcliffe Hospital
Oxford OX3 9DU
UK

1. Umpleby HC, Britton DC, Turnbull AR. Secondary arterio-enteric fistulae: a surgical challenge. *Br J Surg* 1987; 74· 256–9.

Anorectal myectomy for outlet obstruction

Sir

Yoshioka and Keighley presented an interesting study comparing the results of anorectal myectomy and anal dilatation in patients presenting outlet obstruction (*Br J Surg* 1987; 74: 1125–9). Without mentioning other therapeutic approaches, the authors concluded that anorectal myectomy seems to play a therapeutic role in this pathology We cannot agree with this statement for the following reasons. anorectal myectomy is not a causal treatment for this functional pelvic floor disorder; patients may become incontinent soon or later after this procedure; a follow-up of some months or even a year is not long enough; the patient selection can be criticized.

Outlet obstruction may be due to mechanical blockage of the anal canal, to an inadequately or non-relaxing internal sphincter, to scybalous stool or to non-relaxation of the pelvic floor at defaecation. According to the authors, four cases with Hirschsprung's disease have been included. Although a recto-anal inhibitory reflex could be demonstrated, rectal biopsy showed aganglionosis in all these cases. The level at which biopsies were taken is not given. This, however, is of critical importance as a hypo- or aganglionic zone is present at the anorectal junction in normal subjects.[1] Although the recto-anal inhibitory reflex can be falsely positive in Hirschsprung's disease, it might be that the four cases included in this study presented insufficient internal sphincter relaxation, a pathology frequently observed in constipated children[2]. In such cases anorectal myectomy or internal sphincterotomy can only be advocated if conservative treatment fails

Difficult rectal evacuation may also be due to scybalous stool. An inverse relationship between the expulsion effort and the size of simulated stool has been demonstrated[3]. When outlet obstruction is due to non-relaxation of the striated anal and pelvic floor muscles during defaecation, neither myotomy, nor myectomy of the smooth anorectal musculature will influence this functional disturbance. Nevertheless, a permanent reduction of the resistance at the sphincter barrier by whatever procedure will improve the effect of straining. This can be obtained by anorectal myectomy but not by anal dilatation till ± 14 cm anal ring circumference, as we reported recently[4] But if anorectal myectomy would fail, e g. owing to slow colon transit, incontinence for liquid stool could follow colectomy as the rectal saline infusion test became more positive after anorectal myectomy. If stool consistency remains normal, clinical continence will be undisturbed—as happened probably in the two reported cases.

Anorectal myectomy can only be expected to be effective if patients with high anal basal tone are selected. However, several patients with low anal basal pressure can be identified in the scattergram (*Figure 1*). Finally, according to the results of the pre-operative rectal saline infusion test, even patients incontinent for liquids have been included in this study.

So, anorectal myectomy can not be considered a first choice procedure especially in unselected or inadequately selected patients with outlet obstruction. Such patients should first be treated by biofeedback[5]. Naturally, concomitant slow colon transit has to be corrected. If defaecation training fails, anorectal myectomy can still be considered and probably is the procedure of choice in cases with high anal basal pressure.

B. Lestar
F. Penninckx

University Clinic Gasthuisberg
B-3000 Leuven
Belgium

1. Aldridge RT, Campbell PE. Ganglion cell distribution in the normal rectum and anal canal. A basis for the diagnosis of Hirschsprung's disease by anorectal biopsy. *J Pediatr Surg* 1968; 3: 475–90.
2. Loening-Baucke VA. Abnormal rectoanal function in children recovered from chronic constipation and encopresis. *Gastroenterology* 1984; 87: 1299–304.
3. Bannister JJ, Gibbons CP, Trowbridge EA, Read NW Experimental support for a simple model of defaecation. *Gut* 1985; 26: A1131.
4. Lestar B, Penninckx F, Kerremans R. How I do it: anal dilatation *International Journal of Colorectal Disease* 1987, 2: 167–8.
5. Bleiyenberg G, Kuypers HC. Treatment of the spastic pelvic floor syndrome with biofeedback. *Dis Colon Rectum* 1987, 30: 108–11.

Authors' reply

Sir

We wish to reply to the interesting comments made by the Leuven group on the place of anorectal myectomy for outlet obstruction.

(1) We have followed up 34 consecutive patients for more than 2 years, none are incontinent and 17 still open their bowels more than 3 times a week without laxatives.

(2) We agree that outlet obstruction is multifactorial in aetiology and the term may be misleading.

(3) Evidence of aganglionosis was only sought in the proximal 7 cm of the 10-cm strip. Aganglionosis was never confined to the distal segment.

(4) The recto-anal inhibitory reflex is unreliable in identifying short segment Hirschsprung's disease: there are false positives and in our experience the reflex may be absent in incontinence, perineal descent and rectal prolapse.

(5) We agree that anorectal myectomy should be confined to patients with normal colonic transit, increased anal pressure during defaecation and impaired rectal emptying.

(6) If a patient has outlet obstruction and slow transit constipation, subsequent colectomy may be needed after anorectal myectomy. We have 16 such patients, only one is incontinent, but she did have evidence of pudendal nerve neuropathy from straining and we would not now advise anorectal myectomy in such cases

(7) Low resting pressure *per se* is not, in our opinion, a contra-indication to anorectal myectomy and incontinence during the saline infusion test is recorded in some of our normal controls.

We hope these statements help to clarify the place of anorectal myectomy for outlet obstruction.

M. R. B. Keighley
K. Yoshioka

The General Hospital
Birmingham B4 6NH
UK

Role of osmolarity in TPN-associated hepatobiliary dysfunction

Sir

I have read with interest the paper by Truskett *et al.* (*Br J Surg* 1987; **74**: 639–42) and the correspondence in response to this paper by Gouma *et al.* (*Br J Surg* 1987; **74**: 1188). I have also read the answer to the above correspondence by Truskett *et al.* (*Br J Surg* 1987; **74**: 1188). A decrease in bile flow and sludge formation has been noted in pigs when the total parenteral nutrition (TPN) solution was infused intravenously or intragastrically[1]. The daily injection of cholecystokinin in pigs receiving intravenous infusion of TPN did not prevent hepatobiliary dysfunction[1]. Doty *et al.* have shown that daily injection of cholecystokinin octapeptide (5 ng kg^{-1} min^{-1} for 10 min) prevents TPN-induced gallbladder stasis[2]. But in this study gallbladder stasis was assessed by the ratio of gallbladder to hepatic bile ^{3}H-cholic acid specific activity; and the definitive study of prophylaxis of gallstone formation was not done. The solutions used in the TPN are hyperosmolar (1800–2400 mosmol/l)[3]. Intravenous injection of hypertonic glucose solution causes a decrease in bile flow[4]. Blood and bile are isotonic and changes in osmotic pressure of blood are followed by parallel changes in osmotic pressure of bile[5]. Haberich *et al* have shown the existence of osmoreceptors in the portal vein or liver[6]. Reversal of abnormalities in liver function often follows replacement of continuous TPN with cyclic TPN[7,8]. TPN-induced cholestasis occurs more frequently with high calorie and nitrogen intake which usually require more hyperosmolar solutions[9]. In guinea-pigs, intravenous infusion of TPN produces a decrease in hepatic bile flow and this is associated with an increase in bile osmolality[10]. In patients receiving TPN, hypocaloric (500 kcal day^{-1}) oral fluid intake prevents liver function abnormalities[11]. High output fistulae usually produce more than 200 ml fluid per day and this fluid is rich in electrolytes[12]. Re-infusion of fluid from high output fistulae into the distal stoma of patients receiving TPN produces normalization of liver function abnormalities as reported by Gouma *et al.* (*Br J Surg* 1987; **74**: 1188). This is likely to be due to the enteral infusion of fluid containing electrolytes and biliopancreatic secretions leading to an increase in the intestinal motility and release of gastrointestinal hormones.

Thus TPN-associated hepatobiliary dysfunction is likely to be due to hyperosmolar solutions used in the TPN and continuous infusion of TPN, in addition to the absence of enteral stimulation and release of gastrointestinal hormones.

M. V. Math

National University Hospital
Singapore

1. Morgan WP, Truskett PG, Rose MA, Ham JM. Is TPN related hepato-biliary dysfunction secondary to deprivation of enteral stimulation? *Gut* 1986; **27**: A1271.
2. Doty JE, Pitt HA, Porter-Fink V, Denbesten L. Cholecystokinin prophlaxis of parenteral nutrition induced gallbladder disease. *Ann Surg* 1985; **201**. 76–80.
3. Dudrick SJ, Duke JH. Parenteral nutrition—intravenous hyperalimentation. In: Bockus HL, Berk EJ, Hallbrich WS, Kalser M, Roth JLA, Vilardell F, eds. *Gastroenterology*, 3rd ed, Vol. 2. Philadelphia: W.B. Saunders Company, 1972; 395–416.
4. Jacobi M, Zuckerman JC, Kogut B, Klein B. Influence of metabolizable and non-metabolizable sugars on liver bile secretion. *American Journal of Digestive Diseases* 1940; **VII**: 382–5.
5. Gilman A, Cowgill GR. Osmotic relations between blood and body fluids. IV. Pancreatic juice, bile and lymph. *Am J Physiol* 1933; **104**: 476–9.
6. Haberich FJ, Aziz O, Nowacki PE. Übereinen Osmoreceptorish tatigen mechanismus in der leber. *Pfluegers Arch* 1965; **285**: 73–89.
7. Maini B, Blackburn GL, Bistrian BR *et al.* Cyclic hyperalimentation: an optimal technique for preservation of visceral protein. *J Surg Res* 1976; **20**: 515–25.
8. Fleming CR, Beart RW, Berkner S, McGill DB, Gaffron R. Home parenteral nutrition for management of the severely malnourished adult patient. *Gastroenterology* 1980; **79**: 11–18.
9. Cano N, Gerolami A. Intrahepatic cholestasis during total parenteral nutrition. *Lancet* 1983; **i**: 985.
10. Math MV, LaBrooy SJ, Yeoh TS, Jacob E. Effect of total parenteral nutrition (TPN) on bile secretion in guinea pigs. *Aust NZ J Med.* 1983; **13**: A429
11. Pallares R, Sitges-Serra A, Fuentes J, Sitges-Creus A, Guardia J. Cholestasis associated with total parenteral nutrition. *Lancet* 1983; **i**: 758–9.
12. Reber HA. Abdominal abscesses and gastrointestinal fistulas. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management.* 3rd ed. Vol. 1. Philadelphia: W.B. Saunders Company, 1983; 319–35.

Pain in chronic pancreatitis

Sir

We read with interest the article by Pain and Knight comparing two different anastomotic techniques for the relief of pain in chronic pancreatitis (*Br J Surg* 1988; **75**: 220–2). However, we take issue with their conclusion that pancreaticogastrostomy is the treatment of choice for those with ductal dilatation. As Moossa has pointed out in his recent review[1], the rationale for ductal drainage procedures is obscure, since there is no conclusive proof that pancreatic ductal pressures are high in this disease. What is known is that early attempts at drainage by Du Val failed owing to the small size of the anastomosis[2]—a situation the authors have recreated by their short anastomosis over a T tube. Longitudinal pancreaticojejunostomy requires the opening of at least 10 cm of the pancreatic duct, removal of any calculi and a long anastomosis. Subsequent endoscopic retrograde pancreatography shows that this type of anastomosis will remain patent for at least 1 year and probably much longer[3]. Any comparison of two techniques should therefore be with this established operation

Drainage operations can fail for several reasons which the authors' technique seems unlikely to avert. Stenosis may complicate any anastomosis but must surely be commoner if it is short. Indeed, Pain and Knight attribute their failures to this problem, but they have not undertaken pancreaticojejunostomy in a manner designed to prevent it. Since chronic pancreatitis is a progressive disease, further areas of stricture can arise; these will have been anticipated by standard pancreaticojejunostomy and not by pancreaticogastrostomy. Extraction of ductal calculi is easier and more complete after a long ductal split.

There is little to choose between the two procedures with regard to safety. Pancreaticojejunostomy need not be a difficult operation, and the fibrotic gland takes sutures easily. Pancreaticogastrostomy in the authors' hands had a 10 per cent incidence of life-threatening complications. We are interested to note that they routinely perform an operative pancreatogram since we have also found that endoscopic retrograde pancreatography may incorrectly estimate the extent of the disease[4]—yet their paper does not tell us whether the information gained from operative pancreatography ever altered their management.

Pain and Knight are to be congratulated on the results they have achieved with pancreaticogastrostomy. Nevertheless, we feel it is too soon to discard the well-tried operation of longitudinal pancreaticojejunostomy, which we and others have found very satisfactory[3-5].

M. J. Cooper
R. C. N. Williamson*

Bristol Royal Infirmary
Bristol BS2 8HW and
**Hammersmith Hospital*
London W12 0NN
UK

1. Moossa AR. Surgical treatment of chronic pancreatitis an overview *Br J Surg* 1987; **74**: 661–7.
2. Du Val MJ. Caudal pancreatico-jejunostomy for chronic relapsing pancreatitis. *Ann Surg* 1954; **140**: 775–85.
3. Warshaw AL, Popp JW Jr, Schapiro RH. Long-term patency, pancreatic function and pain relief after lateral pancreatico-jejunostomy for chronic pancreatitis. *Gastroenterology* 1980; **79**: 289–93.
4. Cooper MJ, Williamson RCN. Drainage operations in chronic pancreatitis *Br J Surg* 1984; **71**: 761–6.
5. Prinz RA, Greenlee JB. Pancreatic duct drainage in 100 patients with chronic pancreatitis. *Ann Surg* 1981; **194**: 313–20.

Exposure of the facial nerve

Sir

I was interested to read the paper by Mr H.H. Lawson (*Br J Surg* 1988, **75**: 309) showing the value of the tympanomastoid fissure in the exposure of the facial nerve at an early stage in the operation of superficial parotidectomy.

For many years I have used the technique of Oliver Beahrs of the Mayo Clinic to find the main trunk of the facial nerve after it leaves the stylomastoid foramen. He described his method as follows: 'The lowermost tip of the mastoid process can be palpated easily through the insertion of the sternocleidomastoid muscle. A fingertip is placed on the lateral surface of the process pointing directly forwards. Care is taken that the inferior surface of the digit lies flush with the tip of the mastoid. The trunk of the facial nerve will be found deep and slightly anterior to the centre of the fingertip so placed, and thus, the operator's critical attention may be focused in a limited zone of about 1 cm'[1]. The nerve lies at a depth of approximately 1·25 cm.

I have found this method invaluable in 206 operations for superficial parotidectomy and very rarely has there been any difficulty—except in the occasional situation where the tumour involves and overlies the posterior margin of the parotid on to the upper sternomastoid muscle.

The styloid process, which lies deep to the nerve, has been described as a landmark to identify the facial nerve as an initial step. Even this bony structure can be difficult to find as it is absent in 30 per cent of specimens, and it is so small as to be covered by its sheath in another 20 per cent[2]. Even in the remainder, according to Beahrs[1], it can be palpated or visualized only after considerable dissection in a critical zone.

In perusing this article by Mr Lawson, and having examined a number of specimen skulls, I find it extremely difficult to understand how one could feel, never mind see, the vaginal process (sheath of the styloid process[3]) of the tympanic bone without a lot of unnecessary dissection in an area where hazards await the unwary. Also, the typanomastoid fissure is obscured by the strong tendon of the sternocleidomastoid muscle which is inserted into the lateral surface of the mastoid process from its apex to its superior border. In such situations, it is my opinion that one would need to have extremely sensitive fingers—not to mention a gloved finger—in order to feel these rather tenuous structures.

While I welcome Mr Lawson's original contribution in a rather sceptical and critical manner, I do intend to give his method a 'run' in my next parotidectomy. I am convinced, however, that the more practical and much safer technique advocated by Beahrs will be my constant companion.

H. J. Browne

Richmond Hospital
Dublin
Eire

1. Beahrs OH, Adson M. The surgical anatomy and technic of parotidectomy *Am J Surg* 1958; **95**: 885–96.
2. Davis RA, Anson BJ, Budinger JM, Kurth LE. Surgical anatomy of the facial nerve and parotid gland based upon a study of 350 cervico-facial halves. *SGO* 1956; **102**: 385–412.
3. Gray H. *Gray's Anatomy*, 36th edition. Edinburgh: Churchill Livingstone, 1980.

Acute small bowel obstruction

Letter 1

Sir

We read with interest the article by Huddy and Bailey concerning peritoneal encapsulation as a rare cause of acute small bowel obstruction (*Br J Surg* 1988; **75**: 262). We have encountered two very similar cases in recent months.

Case 1. A 23-year-old theatre orderly presented with a 2-day history of severe colicky periumbilical abdominal pain accompanied by profuse vomiting. The clinical and radiological pictures were of small bowel obstruction Hernial orifices were intact and there had been no previous surgery. There was a past history of recurrent mild episodes of periumbilical colic. At laparotomy a loop of ileum was found to have herniated through a defect near the root of the mesentery and was lying in a sac bounded by peritoneum and the left colon. The anatomy was restored to normal and the thickened neck of the sac divided. No resection was required and his postoperative course was unremarkable.

Case 2. A 60-year-old previously well man was referred as an emergency after the sudden onset of severe central abdominal colic associated with vomiting. Past medical history was not relevant He initially settled with conservative management but 2 days later his symptoms recurred immediately following a barium enema. At laparotomy a loop of terminal ileum was seen to be lying in an accessory peritoneal sac on the left side of the abdomen. The hernia was reduced and the bowel was found to be partially necrotic where it had been constricted by the thickened, narrowed neck of the sac. A segmental small bowel resection was performed and the neck of the sac divided. Postoperative recovery was uncomplicated and the patient has remained symptom free since.

Mr Huddy and Mr Bailey state that their patient is the first reported case of acute small bowel obstruction due to peritoneal encapsulation. In the light of our recent experience we wonder if this reflects either a failure to recognize previous cases or a lack of reporting rather than a true rarity of the condition.

J. R. McGregor
G. Ramsay

Western Infirmary
Glasgow G11 6NT
UK

Letter 2

Sir

I do not agree with Messrs Huddy and Bailey (*Br J Surg* 1988; **75**: 262) about two points in their report.

Firstly, 'small bowel obstruction due to peritoneal encapsulation' has already been reported many times but under the more usual name of paraduodenal hernia and 50 per cent of these anomalies would present as acute small bowel obstruction

Secondly, 'removal of the sac' cannot be so simple especially when 'dividing the thickened neck' because this neck can contain the inferior mesenteric vein and left colic artery.

J. Testart

Hôpital Charles-Nicolle
76031 Rouen Cedex
France

Authors' reply

Sir

Thank you for the opportunity to reply to Dr Testart's letter. In a left paraduodenal hernia the anterior margin of the neck of the sac is made up by the inferior mesenteric vein and the colic vessels lie anterior to the sac[1]. This is in keeping with the proposed aetiology of this condition: that the small bowel becomes enclosed behind the left colon mesentery as the gut returns to the abdomen during fetal life. In our case the sac lay anterior to the colonic vessels and the inferior mesenteric vein was not present in the neck of the sac. We therefore feel that this is a separate entity from paraduodenal hernia.

S. P. J. Huddy
M. E. Bailey

1. Davis R. Surgery of left paraduodenal hernia *Am J Surg* 1975, **129**: 570–3.

Modern treatment of varicose veins

Sir

In his leading article, Eklof (*Br J Surg* 1988; **75**: 297–8) dismisses the need for laboratory investigation of patients with varicose veins, and discusses operative management at length. He admits that clinical and Doppler examination alone may be misleading but states that venography and vascular laboratory investigation are seldom required. Research from St. Thomas' Hospital confirms that neither clinical examination or ascending venography provide an accurate assessment of venous function in the lower limb. This can be achieved by using non-invasive means of assessment[1].

We would agree that patients with primary varicose veins can be adequately assessed by clinical examination, especially if aided by Doppler ultrasound A significant proportion of patients present with recurrent or secondary varicose veins, many with skin changes or frank ulceration suggestive of deep venous disease. It is important to determine the venous function in these patients since many will have venous abnormalities that are surgically correctable. While it may be appropriate to consider Duplex ultrasound imaging for patients undergoing venous reconstruction, less complex investigations carried out in the clinic are probably sufficient in the majority of cases[2].

We feel that 'Modern treatment of varicose veins' should be undertaken in the light of full anatomical and physiological knowledge of the venous system.

P. D. Coleridge Smith
J. H. Scurr

The Middlesex Hospital
London W1
UK

1. Stacey MC, Burnand KG, Pattison M, Thomas M Lea, Layer GT. Changes in the apparently normal limb in unilateral venous ulceration. *Br J Surg* 1987; **74**: 936–9.
2. Coleridge Smith PD, Scurr JH. The development of an automated vascular laboratory. *Internat Angiol* 1986; **5**: 253–61.

Book reviews

Common Abbreviations in Clinical Medicine

K. Haber. 175 × 115 mm. Pp. 239. 1988. New York: Raven Press. $19.00.

This tiny volume is packed with abbreviations which the author considers are in common use in clinical medicine. As an editor of a journal which has recently published an announcement denigrating the use of abbreviations, I have to be extremely cautious in my appreciation of this volume. Its first 95 pages constitute a list of abbreviations used in clinical medicine. There are approximately 35–40 abbreviations on each page and this appalling statistic reveals the hold which abbreviations have taken on our profession Some may point to the fact that the author is North American but the same phenomenon is undoubtedly at work on both sides of the Atlantic. Many of the abbreviations are a potential source of confusion. For example, Ab means antibody whereas Ab. means abortion. Similarly Abd means abdomen whereas Abd. means abduction. AFB can mean either acid fast bacillus or aortofemoral bypass, although I must admit that the two are unlikely to be confused BPR means blood per rectum, BRB means bright red blood and it will come as no surprise to our readers that BRBPR means bright red blood per rectum. Numerous other examples which take the use of abbreviations close to the absurd could be cited.

I must now dispel any remaining doubts about my own bias and declare my abhorrence of the use of abbreviations in medicine. The fascist within me would like to see such books burned at a large public ceremony but the realist in me suggests that this small volume may sell quietly and well at least in North America. I will not buy it personally but I suspect that it will be well used within our editorial office, if only to decipher truncated contributions to the Journal.

D. C. Carter

St. Mungo Professor of Surgery,
University of Glasgow
UK

A Manual on Clinical Surgery. Second Edition

S. Das. 182 × 248 mm. Pp. 398. Illustrated. 1987. Calcutta: Dr S. Das.

This book, written and published by one of Calcutta's senior surgeons, bears the stamp of a master teacher. It is illustrated by a set of remarkable photographs of clinical conditions and these monochrome and colour prints, along with reproductions of radiographs and line drawings, amount to nearly 600 illustrations. These will probably be the main source of interest to the western medical student who is unlikely to see such advanced pathology in the clinics where he is taught. Because of limitations in paper and printing, their quality is uneven but their range is fascinating and they stand up well in illustrating a text which is written in a forthright and lively manner.

It is important to emphasize that the book's title may give an exaggerated idea of its scope for it is, in fact, a manual of diagnosis. In the main, it is of general surgical and related problems that the author writes, but a third of the text is devoted to orthopaedic conditions—a conjunction now unfamiliar to the western undergraduate who should be alert, also, to some of the pitfalls of the author's didactic approach.

All in all, the author is to be congratulated for this book; it is one which will undoubtedly be highly regarded in India and a subject of interest elsewhere

J. B. McFarland

Consultant Surgeon
Royal Liverpool Hospital
Liverpool
UK

Adenocarcinoma of the Prostate

A. W. Bruce and J. Trachtenberg. 166 × 247 mm. Pp 213. Illustrated. 1987. New York: Springer Verlag. £50.00.

This book is published in the series *Clinical Practice in Urology* under the general editorship of Professor Geoffrey Chisholm. It is edited by authors based in Canada with contributions from both sides of the 49th Parallel.

This very difficult and increasingly important carcinoma is covered from a variety of points of view, including epidemiology, tumour grading and staging with the various imaging techniques now available, and a final chapter on the methodology and controversy surrounding the many clinical trials now in progress.

Treatment is divided into the treatment of the primary tumour, where the old controversy of radical surgery *versus* radiotherapy is given a good airing, and to which the more recent introduction of interstitial radiotherapy has been added. To one trained in, and doubtless influenced by, the conservative British approach, the case for radical surgery remains inconclusive although it must be remembered that such cases are rarely found in clinical practice in the UK as they are nearly always discovered on routine physical examination.

There is a good chapter on hormone therapy in metastatic prostatic carcinoma by John Trachtenberg and, finally, a tentative case made out for the treatment of prostatic carcinoma by chemotherapy

Altogether an authoritative and well balanced review of this most complex of all carcinomas as seen through North American eyes. It is a book that should be on the shelves of every department of urology and radiotherapy for no one treating the disease can fail to learn something from reading it. For those whose time is very limited, most of the chapters have a useful summary at the end. In short, a worthy addition to an excellent series.

J. C. Smith

Consultant Urologist
Department of Urology
Churchill Hospital
Oxford
UK

A Colour Atlas of Transthoracic Repair of Hiatus Hernia

R. Pringle 265 × 195 mm. Pp. 59. Illustrated. 1987 London. Wolfe Medical Publications £19.00.

This is the latest addition in the single procedures series. The author describes, with the aid of operation photographs, the Belsey Mark IV transthoracic repair of hiatus hernia. The various stages of the procedure are very clearly described. The quality of the photographs is excellent.

This book will be very valuable to surgeons in training and also for those practising surgeons who wish to refresh their memories regarding some of the finer details of the operation before embarking upon the procedure.

My only minor criticism is that, even with the excellent quality of the photographs, some of the structures are hard to identify, and a few more line drawings to complement the operative photographs would help to clarify the stages being taken. However this is a minor point and this series is certainly a must for all medical libraries.

C. M. Royston

Consultant Surgeon
Hull Royal Infirmary
Hull
UK

Venous Thrombosis. Causation and Prediction

D. Ogston. 150 × 235 mm. Pp. 234. Illustrated. 1987. Chichester. John Wiley. £26.50.

Professor Ogston has provided a very comprehensive review of the haemostatic mechanism, thrombus formation and the factors influencing this. Congenital and acquired deficiencies in both the clotting and fibrinolytic systems are covered, with extremely comprehensive bibliographies at the end of each chapter. Many disease states are associated with abnormalities in the clotting system and these are extensively reviewed. The prediction of venous thrombosis forms a relatively minor part of this book but is none the less well presented. The book is readable with explanations of the complex inter-reactions involving the clotting mechanism lucidly explained. The quality of production, with blurring of type and the unfortunate habit of splitting words in inappropriate places, mars an otherwise extremely valuable contribution to this subject.

J. Scurr

Senior Lecturer in Surgery
The Middlesex Hospital
London W1
UK

Surgical Applications of Lasers. Second Edition.

J. A. Dixon. 155 × 234 mm. Pp. 355. Illustrated. 1988. London: Wolfe Medical Publications. £44.50.

The title of this volume is incomplete and should be revised to 'The Surgical Application of Lasers in the United States'. Only one contribution has been invited from outside the USA and this is evident in much of the writing which reflects many financial and organizational aspects that are unique to the American medical system. Despite this rather insular approach the editor has brought together an impressive group of experts. Subjects reviewed include not only the clinical applications but also the basic physics, safety and biological aspects of lasers. In the clinical reviews the standard of objectivity varies and several of the chapters, particularly those on general and endoscopic applications, are best seen as listings of what has been attempted without too much critical review. This is balanced by the much more open approach in the sections on orthopaedic, gynaecological and endobronchial usage. This volume is likely to be purchased only by individuals with a special interest in laser surgery for whom it will provide a rich source of up-to-date references. It is best considered as a reference text which is most appropriately found on a library shelf where it could be of considerable interest to a wide range of readers. Unfortunately laser medicine is a fast moving speciality, it is only 4 years since the first edition and the next will have to be brought out even sooner if the text is to remain relevant and informative.

R. A. Harrison

Senior Registrar in Surgery
Edgware General Hospital
London HA8 0AD
UK

Peripheral Vascular Surgery

W. C. Lamberth and D. B. Doty. 219 × 284 mm Pp 333. Illustrated. 1987. Chicago: Year Book Publications. £58.00.

There are now many atlases of operative vascular surgery and the canny buyer is likely to browse through several before making his choice and parting with his money. Line drawings have been used throughout and are clear and easily understood. The text which the drawings illustrate is always on the facing page so that irritating flipping of pages is eliminated. The book is well set out in sections and the reader can easily locate the operation he is interested in from the list of contents without reference to the index. Not surprisingly in a book from North America, the first operation described is carotid endarterectomy—the sales leader in that free market economy. Indications and contra-indications for this and other operations are scarcely referred to, while the hazards and complications of operations usually rate no mention. The reader will find here any arterial operation he may want to know about, including several I have never seen, but he may be disappointed by the scant account of operations on veins Surely no modern book should have illustrations showing avulsion of varicose veins through transverse incisions large enough to allow the insertion of two rake retractors. One serious illustrative error which the accompanying account does not correct shows the posterior skin flap for a below-knee amputation to be so short that wound closure would be impossible I looked in vain for any of the technical tips which have guided me through the difficult parts of the operations described and which I daily pass on to my grateful registrars. At no point did the text rekindle that feeling of confident excitement felt when being talked through each stage of a new operation by a teacher who can see and anticipate any error before it is made.

J. Collin

Consultant Surgeon
John Radcliffe Hospital
Oxford
UK

Notices and announcements

10–14 July 1988
XIIth Biennial Congress of the International Society of University Colon and Rectal Surgeons
Glasgow, UK
Information Secretariat, 1275 South Cedar Crest Boulevard, Allentown, Pennsylvania 18103, USA

14–16 July 1988
XIIIth International Update on Liver Disease
Royal Free Hospital, London, UK
Information: Professor N. McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

27–31 July 1988
International Symposium of Inflammatory Heart Disease. A Multidisciplinary Approach to Myocarditis and Heart Allograft Rejection
Colerado, USA
Information: Ms Marge Adey, Continuing Education, University of Nebraska Medical Centre, 42nd and Dewey Avenue, Omaha, NE 68105-1065 Nebraska, USA

14–19 August 1988
XII International Congress of the Transplantation Society
Sydney, Australia
Information Congress Secretariat, 145 Macquarie Street, Sydney, NSW 2000, Australia

28 August–1 September 1988
Fifth World Conference on Lung Cancer
Interlaken, Switzerland
Information. Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basle, Switzerland

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information· Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

4–8 September 1988
11th Annual Meeting of the European Neuroscience Association
Zurich, Switzerland
Information· 11th Annual Meeting of the European Neuroscience Association, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

8–10 September 1988
Annual Meeting of the Association of Surgeons in Training
Belfast, UK
Information: Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

10–18 September 1988
Fourth Annual Fall Ultrasound Symposia
London, UK
Information: Annual Fall Ultrasound Meeting, Medical Seminars International Inc., 21915 Rosco Boulevard, Suite 222, Canoga Park, California 91304, USA

12–14 September 1988
International Hepatobiliary Pancreatic Association
Nice, France
Information: Dr Jean Mouiel, Department of Surgery, Hôpital Saint Roch–BP319, 06006 Nice Cedex, France

14–16 September 1988
Royal College of Surgeons of England Annual Meeting of Fellows and Members
Cambridge, UK
Information· Secretary, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

14–17 September 1988
9th European Immunology Meeting
Rome, Italy
Information. MGA Via P Cossa, 41 00193 Rome, Italy

18–23 September 1988
The Second Oxbridge Organ Transplantation Course
Cambridge, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1988
Oxford Postgraduate Seminar on Early Intervention in Major Trauma
Oxford, UK
Information: Dr P. Nash, Casualty Surgeons Association, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–30 September 1988
Royal Microscopical Society Ultrastructural Anatomy Course
Belfast, UK
Information· The Administrator, Royal Microscopal Society, 37/38 St. Clements, Oxford OX4 1AJ, UK

5–8 October 1988
4th Congress of the European Society of Surgical Oncology (ESSO 88)
Paris, France
Information· ESSO 88, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France

5–8 October 1988
4 Jahrestagung Der Deutschen Gesellschaft Für Lasermedizin
Vienna, Austria
Information· Doz Dr A. Tuchmann, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Vienna, Austria

20 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information. Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

30 October–1 November 1988
13th Congress of the European Society for Medical Oncology (ESMO)
Lugano, Switzerland
Information. Dr F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

4–7 November 1988
The XXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases
Singapore
Information; Professional Postgraduate Services, K.K., Singapore Representative Office, 20 Kramat Lane #03-07, United House, Singapore 0922

25–26 November 1988
European Symposium on Ultrasonic Radiation Safety
Copenhagen, Denmark
Information: Mrs A G. Thorn, Ultrasound Laboratory, Glostrup Hospital, DK 2600 Glostrup, Denmark

25–27 November 1988
22nd Annual Combined Surgical Meeting
Singapore
Information: The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

8th December 1988
British Association of Surgical Oncology Forum: 'Head and Neck Cancer for the General Surgeon'
London, UK
Information. British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–18 December 1988
Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons
Las Vegas, USA
Information. Dr M. R. Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988
Association of Surgeons of India Golden Jubilee Annual Conference
New Delhi, India
Information: Dr N. C. Madan, Organizing Secretary 'ASICON-88', Room No. 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

The American Journal of Surgery®

JUNE 1988 • VOLUME 155 • NUMBER 6

CONTENTS IN BRIEF

EDITORIAL OPINION

719 **Nonoperative Interventional Therapy in Gallstone-Associated Acute Pancreatitis.** Jose F. Patiño

SCIENTIFIC PAPERS

720 **Sudden Cardiac Arrest in Morbidly Obese Surgical Patients Unexplained After Autopsy.** Ernst J. Drenick and Janis S. Fisler

727 **Cholescintigraphy in the Critically Ill.** Warren L. Garner, M. Victoria Marx, and Peter J. Fabri

730 **Preoperative and Postoperative Medical Evaluation of Surgical Patients.** Robert Gluck, Eric Muñoz, and Leslie Wise

735 **Hemodynamic and Morphologic Alterations After Experimental Administration of Protamine Sulfate.** Julian Alvarez, Lourdes Alvarez, Cristina Escudero, Fernando Gilsanz, Santiago de Oya, and Jose Luis Castillo-Olivares

741 **Thyroglossal Duct Cysts. A Thirty Year Experience With Emphasis on Occurrence in Older Patients.** Alfred D. Katz and Mark Hachigian

745 **Delayed Presentation of Blunt Splenic Injury.** Ari Leppäniemi, Reijo Haapiainen, Carl-Gustaf Standertskjöld-Nordenstam, Matti Taavitsainen, and Junno Hästbacka

750 **Is Routine Triple Endoscopy Cost-Effective in Head and Neck Cancer?** Ashok Shaha, Eddie Hoover, Jose Marti, and Yosef Krespi

754 **Desmoid Tumors in Adults: The Role of Radiotherapy in Their Management.** Jean Pierre Bataini, Claude Belloir, Andre Mazabraud, Jacques Pierre Pilleron, Aude Cartigny, Christian Jaulerry, and Nemetallah A. Ghossein

761 **Surgical Therapy of Radiation-Induced Lesions of the Colon and Rectum.** Johannes Miholic, Christian Schwarz, and Peter Moeschl

765 **Protein Leak From Normal Vasculature Due to Human Malignant Ascites.** Louis S. Heuser, Frederick N. Miller, and Catherine Gilley-Pietsch

770 **Influence of Preoperative Risk Factors and the Surgical Procedure on Surgical Mortality in Renovascular Hypertension.** Johan H. van Bockel, Reinout van Schilfgaarde, Willem Felthuis, Jo Hermans, and Johan L. Terpstra

776 **Shotgun Wounds Involving the Head and Neck.** W. Reid Grimes, Don M. Morris, and Edwin A. Deitch

780 **Nonoperative Removal of Giant Common Bile Duct Calculi.** Shinji Matsumoto, Seiyo Ikeda, Masao Tanaka, Hideo Yoshimoto, and Fumio Nakayama

HOW I DO IT

783 **Stapling Techniques for Easy Construction of an Ileal J-Pouch.** J. Preston Hughes, A. Robert Bauer, Jr., and Charles M. Bauer

786 **Cause and Prevention of Postherniorrhaphy Neuralgia: A Proposed Protocol for Treatment.** Irving L. Lichtenstein, Alex G. Shulman, Parviz K. Amid, and Michele M. Montllor

REVIEW

791 **Rehabilitation of the Cancer Patient.** Scott H. Kurtzman, Bernard Gardner, and Wendy S. Kellner

EDITORIAL COMMENT

744 **Further Thoughts on Thyroglossal Duct Cysts.** Carl Davis, Jr.

804 **Book Reviews**

805 **Letters to the Editor**

806 ***The British Journal of Surgery* Table of Contents (vol. 75, no. 6, June 1988)**

807 **Author Index**

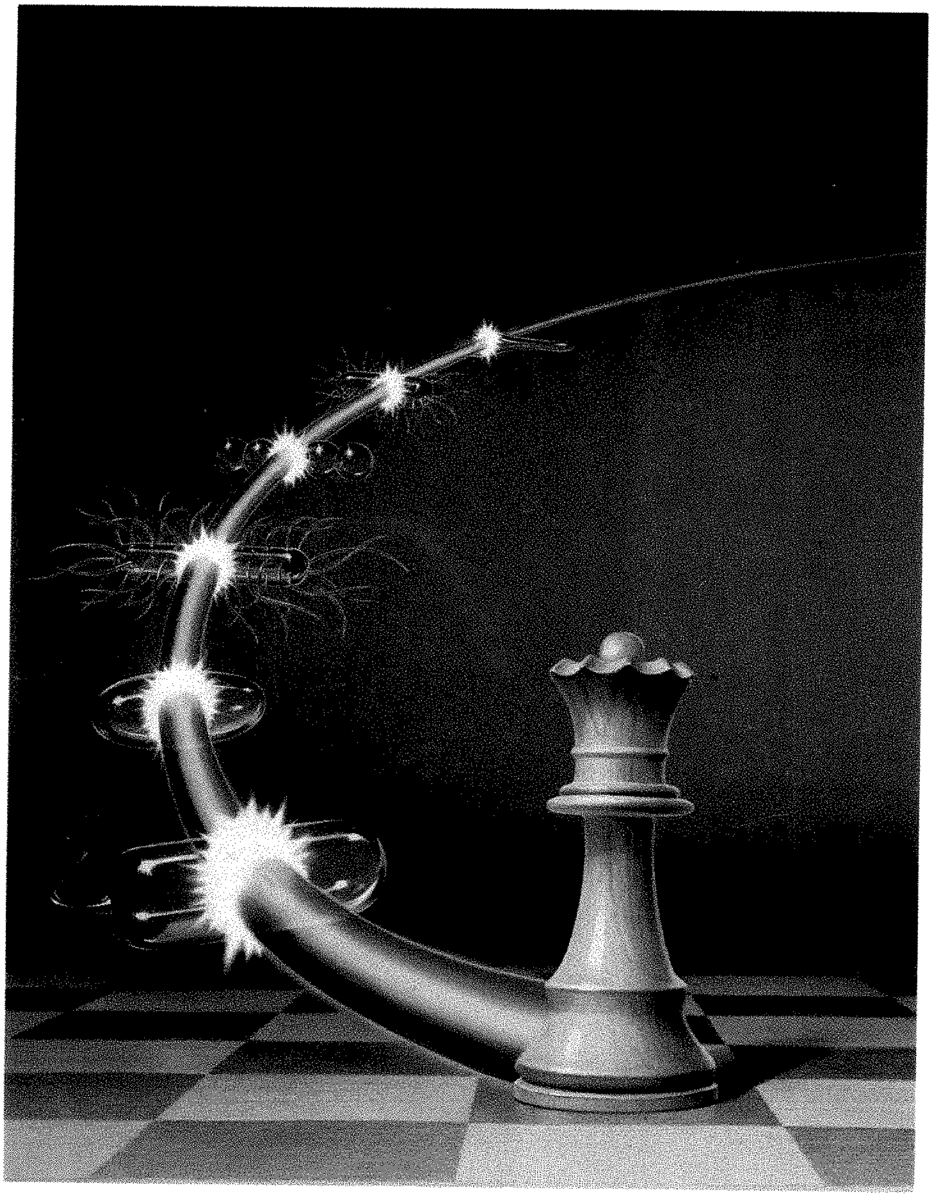
808 **Subject Index**

A20 **Information for Authors**

PIPRIL

INTRAMUSCULAR/INTRAVENOUS PIPERACILLIN

Still a key move in surgical infections



- Proven single agent a
- Broad spectrum cove including anaerobes.[4] A against *Strep. faecalis* unlike cephalosporins, aminoglycosides and metronidazole.
- Highly synergistic wit aminoglycosides[6,7]
- Low potential for indu resistance compare 'third generation' cephalosporins[8,12]
- Effective concentratio bile and peritoneal flu
- Well tolerated[11]

Prescribing Information. **Indications:** Pipril is a broad spectrum bactericidal penicillin for the treatment and peri-operative prophylaxis of systemic or local infections caused by sens **Dosage:** Adult patients with normal renal function should receive 4-8g daily in divided doses for mild or uncomplicated infections. In serious or life-threatening infections 12-16g daily For peri-operative prophylaxis 2g just prior to surgery followed by at least two doses of 2g at four or six hour intervals. Patients with renal insufficiency may need dosage reduction Children 2 months to 12 years of age: 100-300 mg/kg daily in three to four divided doses. Neonates and infants under two months of age: 100-300 mg/kg daily in two equally divided **Contra-indications:** Penicillin or severe cephalosporin hypersensitivity. **Precautions:** Safety for use in pregnant or lactating women has not yet been established. **Side effects:** Uncom of injectable penicillins. **Administration:** Pipril is presented as 1g or 2g vials, 4g infusion bottles and 4g infusion packs containing piperacillin as piperacillin sodium. See Data Sheet for full details of preparation and administration. **Product Licence No.** 0095/0073. **Basic NHS Price:** 1g vial £2.98, 2g vial £5.90, 4g infusion bottle £11.66. 4g infusion pack (4g bo needle) £12.43. Further information is available on request.

References

1. Wittmann, D.H., *et al.*, Proc. 21st ICAAC, 1981: 404. 2. Fredlund, H., *et al.*, Proc. 12th ICC 1981, **1,** 700. 3. Morris, D.L., *et al.*, *J. Hosp. Inf.* 1983, **4:** 159-164. 4. Leigh, D.A., *J. An Chemother.* 1984, **13,** 525-567. 5. Nicoletti, P., *Drugs Exper. Clin. Res.*, 1983, **9** (8-9): 609-624. 6. Hoogkamp-Korstanje, J.A.A., *et al.*, *J. Antimicrob. Chemother.* 1981, **8,** 101-106. 7. 2nd Int. Symp. Infec. Immunocomp. Host 1983, 172-174. 8. Sanders, C.C., *J. Antimicrob. Chemother.*, 1984, **13,** 1-3. 9. Taylor, E.W., *et al.*, *J. Int. Med.*, 1983; **11:** 28-31. 10. Wittma Schassan, H.H., Proc. Piperacillin Symp. (Munich) 1980, 142-152. 11. Pipril Product Information Book. 12. Minami, S., *et al.*, *Antimicrob. Ag. Chemother.*, 1980, **18,** (3), 382-385.

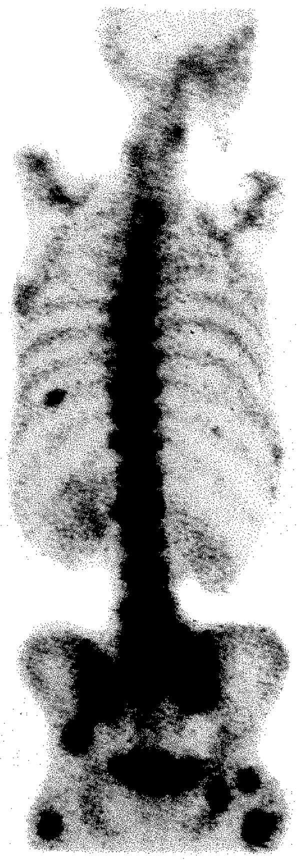
Lederle Laboratories, A division of Cyanamid of Great Britain Limited, Fareham Road, Gosport, Hants PO13 0AS. Tel: (0329) 224000. PIPRIL is a trademark

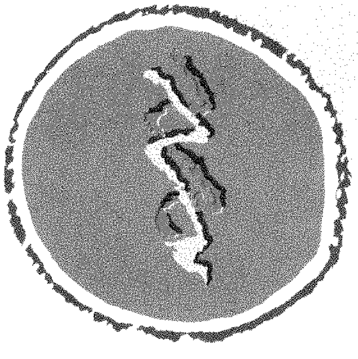
e British
urnal of Surgery

e 75, Number 8, August 1988

Acc.
26.8.88

LIBRARY





When tamoxifen fails

Farlutal achieves remissions

With rapid relief of bone pain

ABBREVIATED PRESCRIBING INFORMATION Before prescribing Farlutal please refer to the full data sheet. PRESENTATION Tablets of 100,250 or 500mg. Vials of 500 or 1000mg (200mg/ml) medroxyprogesterone acetate. INDICATIONS Palliative treatment of hormone-sensitive malignancies. DOSAGE Breast Carcinoma: 1000-2000mg daily, orally. Alternatively, 500-1000mg/ day i.m. for 4 weeks initially and 500mg i.m. bi-weekly for maintenance. Endometrial and Prostatic Carcinoma: 500mg i.m. twice weekly then 500mg i.m. weekly as maintenance or 100-500mg orally. Renal Adenocarcinoma: 500mg i.m. on alternate days for 30 days, then 500mg i.m. bi-weekly to 60th day, then 250mg i.m. weekly, or 100-500mg/day orally. CONTRA-INDICATIONS Thrombophlebitis, thrombo-embolic disorders, severe hepatic insufficiency, hypercalcaemia (osseous metastases), suspected or early breast carcinoma, missed abortion, metrorrhagia, pregnancy. Hyper-sensitivity to hydroxybenzoates (i.m. formulation only). WARNINGS AND PRECAUTIONS Discontinue treatment after thrombo-embolic episodes, migraine or ocular problems. Care in diabetes or hypertensives. Rarely congenital cardiac malformation in the neonate, and masculinisation of female foetuses can occur after use in pregnancy. Malignant mammary nodules have occasionally been seen in beagle dogs although their relevance to humans is not known. SIDE EFFECTS After i.m. injection local lesions can occur which may be minimised by injecting deeply into healthy gluteal muscle. Progestogenic and adrenergic-like tremor reactions have been reported. Corticoid-like effects may also occur. Cholestatic jaundice has occasionally been reported. LEGAL CATEGORY POM. PACKAGE QUANTITIES, BASIC NHS PRICE AND PRODUCT LICENCE NUMBERS 100 x 100mg tablets – blister strips. £34.00 3433/0056. 50 x 250mg tablets – blister strips. £40.00 3433/0058. 56 x 500mg tablets – blister strips (calendar pack). £87.75 3433/0080. 500mg vial for injection £12.00 3433/0045. 1000mg vial for injection £20.00 3433/0045. FURTHER INFORMATION AND DATA SHEETS ARE AVAILABLE ON REQUEST FROM: Farmitalia Carlo Erba Ltd., Italia House, 23 Grosvenor Road, St. Albans, Herts AL1 3AW

Farlutal ***500 b.c***

medroxyprogesterone acetate

A second chance for patients with advanced breast can

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Volume 75 Number 8 August 1988

LEADING ARTICLES

Surgical nutrition: time for some clinical common sense 729
G. L. Hill
Acute surgical disease and scoring systems in daily surgical practice 731
M. Schein

Abdominal aortic aneurysm 733
P. R. S. Thomas and R. D. Stewart
Use of skin staples for fashioning colostomies (surgical workshop) 736
R. M. Antrum and J. J. Price
Femorodistal vein bypass graft stenoses 737
M. J. Grigg, A. N. Nicolaides and J. H. N. Wolfe
Human gastric perfusion: evidence for non-uniformity of blood flow 741
P. I. M. Allen, I. Chesner, K. Wheatley and M. Goldman
Reproducibility of reactive hyperaemia test in the measurement of peripheral arterial disease 743
F. G. R. Fowkes, E. Housley, C. C. A. Macintyre, R. J. Prescott and C. V. Ruckley
Endoscopic sclerotherapy in the treatment of gastric varices 747
S. K. Sarin, G. Sachdev, R. Nanda, S. P. Misra and S. L. Broor
Trial of sclerosing agents in patients with oesophageal varices 751
S. Kitano, Y. Iso, H. Yamaga, M. Hashizume, H. Higashi and K. Sugimachi
Intramural haematoma of the alimentary tract in children 754
S. Chittmittrapap, B. Chandrakamol and S. Chomdej
Perforated gastric ulcer 758
C. Lanng, C. Palnæs Hansen, A. Christensen, C. S. Thagaard, M. Lassen, A. Klærke, H. Tønnesen and S. E. Ostgaard
Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus 760
C. S. Robertson, J. F. Mayberry, D. A. Nicholson, P. D. James and M. Atkinson
Enucleated parotid tumours 764
J. D. Maynard
Use of older patients as cadaveric kidney donors 767
M. C. Foster, P. W. Wenham, P. A. Rowe, R. W. Blamey, M. C. Bishop, R. P. Burden and A. G. Morgan
DNA ploidy pattern and tumour spread in gastric cancer 770
X. de Aretxabala, Y. Yonemura, K. Sugiyama, T. Kamata, K. Konishi, K. Miwa and I. Miyazaki
Reconstruction after excision of soft tissue sarcomas of the limbs and trunk 774
A. Stotter, N. R. McLean, M. E. Fallowfield, N. M. Breach and G. Westbury
Assessment of the analgesic efficacy of nefopam hydrochloride after upper abdominal surgery: a study using patient controlled analgesia 779
T. T. C. McLintock, G. N. C. Kenny, J. C. Howie, C. S. McArdle, S. Lawrie and H. Aitken
Prophylactic antibiotics in elective colorectal surgery 782
W. Y. Lau, K. W. Chu, G. P. Poon and K. K. Ho
Pre-operative diagnosis of non-strangulated obturator hernia: the contribution of herniography (case report) 785
L. A. Carriquiry and A. Piñeyro
Delayed external sphincter repair for obstetric tear 786
S. Laurberg, M. Swash and M. M. Henry

LIBRARY

BOOKS FROM BUTTERWORTHS

Rob and Smith's **Operative Surgery**

GYNAECOLOGY AND OBSTETRICS · Fourth Edition

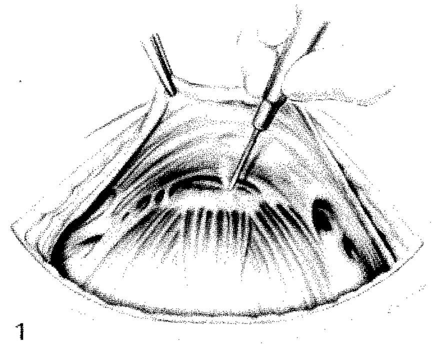
Edited by **John M Monaghan** *FRCS(Ed), FRCOG Consultant Gynaecological Surgeon, Queen Elizabeth II Hospital, Gateshead, UK*

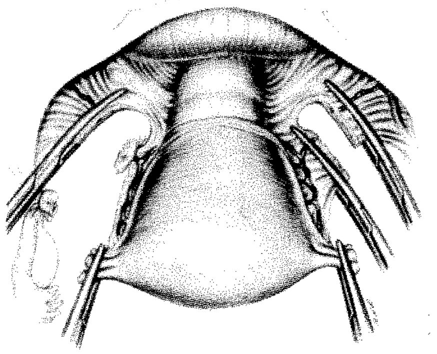
General Series Editors: **Hugh Dudley** *ChM, FRCS(Ed), FRACS, FRCS*
David C Carter *MD, FRCS(Ed), FRCS(Glas)*
R C G Russell *MS, FRCS*

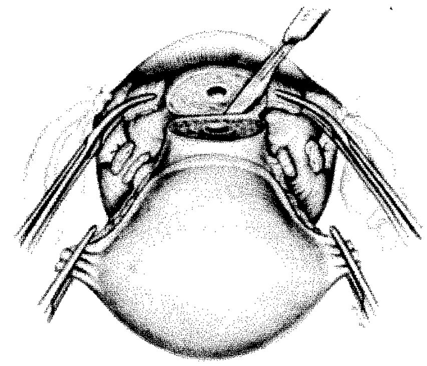
* **Extensively revised and rewritten**
* **New international team of contributors**
* **Illustrations all redrawn by a single artist**

In order to reflect the best of modern practice the fourth edition of this volume in the Operative Surgery series has been completely rewritten and re-illustrated. The new editor has chosen a team of internationally recognised authorities to present their tried and tested approaches to the standard gynaecological operations. The implications of modern suture materials and surgical techniques such as the use of lasers and stapling guns are fully discussed. Also included are the newer diagnostic techniques which now demand the attention of the obstetrician and gynaecologist – chorion villus sampling and fetoscopy, for example. The presentations are complemented by detailed and clear drawings which provide step-by-step instruction to the application of the techniques.

The result is a broad and balanced coverage of all the important procedures which make up the daily practice of the gynaecological surgeon. Like its companions in the Series it will become the indispensable reference to surgical craft for all those in both training and practice.







Contents: Dilation and curettage • **Endometrial sampling and cytology techniques** • **Termination of pregnancy** • Suction • Middle trimester • Hysterotomy • **Operations on the vulva** • Simple vulvectomy • Bartholin's gland, removal and marsupialisation • Fenton's procedure • Urethral prolapse procedures • **Surgical treatment of CIN** • Electrocautery • Laser ablation • Cryosurgery • Cold coagulation • Cone biopsy, cold knife and laser • **Laparoscopy** • Diagnostic • Tubal occlusion • Second look • **Tubal ligation** • **Total abdominal hysterectomy** • **Vaginal hysterectomy** • **Operations for genital prolapse** • Anterior and posterior colporrhaphy • Manchester repair • Enterocoele repair • Le Fort procedure • **Operations for bladder dysfunction** • **Surgery of vesicovaginal and rectovaginal fistulae** • **Myomectomy** • **Operations for infertility** • Uteroplasty • Tuboplasty, micro and macrosurgical techniques • Ventrosuspension • **Surgery of endometriosis and pelvic infection** • **Surgery for benign ovarian disease** • **Surgery for malignant ovarian disease** • **Radical (Wertheims) hysterectomy** • **Radical vulvectomy and groin and pelvic node dissection** • **Radical vaginectomy** • **Exenterative surgery** • **Colostomy and urinary bypass procedures** • **Operations for the production of neovaginas** • Williams and McIndoes procedure • Gracilis myocutaneous transplants • Use of bowel transplants • **Laser surgery** • **Stapling techniques in obstetrics and gynaecology** • **Obstetric operations** • D & C evacuation of the uterus • Surgery of ectopic pregnancy • Surgery of recurrent abortion, including MacDonald and Shirodkar suture • Caesarean section • Surgery for the repair of obstetric trauma • Amniocentesis, fetoscopy and chorion villus sampling • Index

December 1987 320 pages 276 x 219 mm Hardcover Illustrated 0 407 00680 X £90.00

Order this title from your bookseller or in case of difficulty from the address below

For details of other Butterworth Scientific titles, please contact the appropriate office.
Orders should be sent to the appropriate office listed below.
The UK headquarters serves all UK and overseas markets except where there is a local Butterworths office.

United Kingdom
Butterworths, Borough Green
Sevenoaks, Kent TN15 8PH
England

Customers in Asia may order through:
Butterworth & Co (Asia) Pte Ltd
30 Robinson Road, Unit 12-01 Tuan Sing Towers
Singapore 0104, Republic of Singapore

USA & Canada
Butterworth Publishers
80 Montvale Avenue
Stoneham, MA 02180, USA

Australia & Papua New Guinea
Butterworths Pty Ltd, PO Box 345
North Ryde, New South Wales 2113
Australia

New Zealand
Butterworths of New Zealand Ltd
33-35 Cumberland Place
Wellington 1, New Zealand

Blood transfusion and infectious complications following colorectal cancer surgery 789
P. I. Tartter

Influence of pancreatic resection on systemic complications in acute necrotizing pancreatitis 793
O. Teerenhovi, I. Nordback and J. Isolauri

Primary anoplasty with skin flaps in posterior sagittal anorectoplasty (surgical workshop) 795
W. D. Ng, Y. T. Chan and H. Fung

Gallbladder non-filling: an indication for cholecystectomy after endoscopic sphincterotomy 796
C. S. Worthley and J. Toouli

Choledochal cyst: a 33 year review 799
J. F. R. Robertson and P. A. M. Raine

Ischaemic atrophy of the cervical portion of a substernal colic transplant: successful reconstruction using a synthetic resorbable tube (case report) 801
D. Gossot and J.-F. Lefebvre

Benign disease of the common bile duct 803
R. Saxena, R. Pradeep, J. Chander, P. Kumar, J. D. Wig, R. V. S. Yadav and S. P. Kaushik

Standardization of the surgical technique in breast-conserving treatment of mammary cancer 807
K. Aspegren, L. Holmberg and H.-O. Adami

Application of mammary serum antigen assay in the management of breast cancer: a preliminary report 811
J. J. Tjandra, I. S. Russell, J. P. Collins, S. A. Stacker and I. F. C. McKenzie

Superior laryngeal nerve injury: an overlooked entity in the surgery of the head and neck (surgical workshop) 817
K. Bevan, M. V. Griffiths and M. H. Morgan

Lympho-epithelial 'branchial' cysts with the parotid gland (case report) 818
A. Wyman, L. K. Dunn, V. R. Talati and K. Rogers

Bilateral spontaneous descent of the testis after the age of 10: subsequent effects on fertility 820
T. Bremholm Rasmussem, H. J. Ingerslev and H. Høstrup

Penetrating injuries of the diaphragm 824
D. Demetriades, S. Kakoyiannis, D. Parekh and C. Hatzitheofilou

A serious complication of the Angelchik prosthesis (case report) 826
N. R. Boeree, C. P. Armstrong, C. Brown and B. Pickering

CORRESPONDENCE **828**

BOOK REVIEWS **831**

NOTICES AND ANNOUNCEMENTS **832**

Cover picture

Lord Lister Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA)

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Editorial Committee

Chairman
C. W. Jamieson, *London*

Vice-Chairmen
J. L. Dawson, *London*
H. B. Devlin, *Stockton-on-Tees*

Editors
R. C. G. Russell, *London*
D. C. Carter, *Glasgow*

Associate Editor
A. E. Young, *London*
Statistical Consultant
G. D. Murray, *Glasgow*
Editorial Secretary
Lynne Ponjee

T. Bates, *Ashford*
K. G. Burnand, *London*
(*Surgical Research Society*)
J. D. Hardcastle, *Nottingham*
A. G. Johnson, *Sheffield*
M. R. B. Keighley, *Birmingham*
J. A. P. Marston, *London*
A. N. Nicolaides, *London*
(*Royal Colleges of Surgeons*)
I. Taylor, *Southampton*
(*Association of Surgeons*)
N. S. Williams, *London*
R. C. N. Williamson, *London*

Editorial Board

A. P. R. Aluwihare, *Sri Lanka*
E. Q. Archampong, *Ghana*
J. H. Baron, *London*
J. Bergan, *USA*
K. Bielecki, *Poland*
H. Bismuth, *France*
P. C. Bornman, *South Africa*
D. Bouchier-Hayes, *Dublin*
W. H. Brummelkamp, *The Netherlands*
R. Carpenter, *Jamaica*
A. Cuschieri, *Dundee*
R. Dionigi, *Italy*
B. Eklof, *Kuwait*
E. A. Elebute, *Nigeria*
J. R. Farndon, *Newcastle upon Tyne*
J. M. Fitzpatrick, *Dublin*
Sir Patrick Forrest, *Edinburgh*
W. D. George, *Glasgow*
G. R. Giles, *Leeds*
I. E. Gillespie, *Manchester*
B. C. Golematis, *Greece*
J. F. Grenier, *France*
A. Habr-Gama, *Brazil*
D. Hanania, *Jordan*
F. Harder, *Switzerland*
M. A. Hassan, *Sudan*
R. J. Heald, *Basingstoke*
G. L. Hill, *New Zealand*
T. Hirayama, *Japan*
M. Horrocks, *Bristol*
E. R. Howard, *London*
L. Hulten, *Sweden*
M. H. Irving, *Manchester*
G. G. Jamieson, *Australia*
J. Jeekel, *The Netherlands*
H.-E. Jensen, *Denmark*
Jin-Pok Kim, *Korea*
K. A. Kelly, *USA*
J. A. Mannick, *USA*
T. G. Parks, *Belfast*
A. Pausawasdi, *Thailand*
C. Pera, *Spain*
H. C. Polk, *USA*
A. T. Raftery, *Sheffield*
N. Rangabashyam, *India*
J. H. C. Ranson, *USA*
C. V. Ruckley, *Edinburgh*
S. Shionoya, *Japan*
J. C. Smith, *Oxford*
K. Somasundaram, *Malaysia*
T. E. Starzl, *USA*
H. Stone, *USA*
D. E. Strandness Jr, *USA*
G. Teasdale, *Glasgow*
M. Trede, *West Germany*
D. E. F. Tweedle, *Manchester*
A. Watson, *Lancaster*
R. W. Webb, *USA*
D. J. T. Webster, *Cardiff*
F R. Wilkes, *Armed Forces*
D. Wilmore, *USA*
J. Wong, *Hong Kong*
R. F. M. Wood, *London*

The British Journal of Surgery is published monthly by Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 300966 Telegrams and Telex 859556 SCITEC G Facsimile 0483 301563 Registered office Butterworth Scientific Limited, 88 Kingsway, London WC2 6AB, UK

All queries regarding submitted papers not yet accepted for publication should be addressed to Lynne Ponjee, Editorial Secretary, Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 301439 Telegrams and Telex 859556 SCITEC G. Facsimile: 0483 301563

Managing Editor Sarah Graham-Campbell
Sub-Editor June Greig-Smith
Production Julia Sentance
Advertisement Sales Representative Mark Butler

UK and Overseas subscription orders should be sent to Westbury Subscription Services, PO Box 101, Sevenoaks, Kent TN15 8PL, UK Telephone 0732 885833 Telex 95678 Facsimile 0732 884079 Cable Westbury, Sevenoaks, Kent **North American orders** should be sent to Journals Fulfilment Department, Butterworths, 80 Montvale Avenue, Stoneham, MA 02180, USA Telex 880052 Telephone (617) 438 8464

The annual subscription to **The British Journal of Surgery** (12 issues) for UK readers is £59 00, single copies £6.00 and personal subscription £47 00 Overseas rates are. annual subscription £70 00, single copies £7 00 and personal subscription £47 00 These prices include delivery by sea mail, air mail rates are available on request For North America rates are annual subscription £70 00, single copies £7 00, personal subscription £47 00 Copies of this journal sent to subscribers in Australasia, Bangladesh, Canada, India, Pakistan, Sri Lanka and USA are air-speeded for quicker delivery at no extra cost

Back Issues prior to the current volume are available from Wm Dawson & Sons Ltd, Cannon House, Folkestone, Kent, England CT19 5EE Telephone 0303 57421

US mailing agents Mercury Airfreight International Ltd Inc Second class postage paid at Rahway, New Jersey, USA Postmaster send address corrections to *The British Journal of Surgery*, c/o Mercury Airfreight International Ltd Inc, 10B Englehard Avenue, Avenel, New Jersey 07001, USA

A microfilm version of **The British Journal of Surgery** is available Please contact University Micro Films Inc, 300 N Zeed Road, Ann Arbor, Michigan, Michigan 48106, USA

Copyright: Readers who require copies (minimum quantity 100) of papers published in this journal may either purchase reprints or obtain permission to copy from the publisher For readers in the USA, permission to copy is given on the condition that the copier pays the stated per copy fee through the Copyright Clearance Center Inc, 27 Congress Street, Salem, Massachusetts 01970, USA (617) 744 3350 for copying beyond that permitted by Sections 107 and 108 of the US Copyright Law Fees appear in the code given at the foot of the first page of each paper This journal is listed in 'Current Contents'.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the Publisher

ISSN 0007-1323

Filmset by Mid-County Press, London SW15 Printed by The Friary Press Ltd, Dorchester and London

Br. J. Surg. 1988, Vol. 75, August, 729–730

Surgical nutrition: time for some clinical common sense

By the nature of their work, gastrointestinal surgeons see a lot of malnourished patients. The number, however, may not be as great as we thought. Donald McLaren, an expert in childhood malnutrition in the Third World, thinks that the incidence of malnutrition in hospital has been exaggerated[1]. He reminds us that childhood protein energy malnutrition may be manifest as a spectrum of disease, the most severe forms of which are marasmus (with extreme wasting of fat and muscle but with normal levels of plasma albumin) and kwashiorkor (with skin changes, oedema, fatty liver and hypo-albuminaemia). Surgical malnutrition is basically of the marasmic type and kwashiorkor is almost unknown in our hospitals. McLaren points out that plasma albumin has therefore been wrongly used as the yardstick with which to measure the incidence of protein-energy malnutrition in hospital. This, together with the fact that many other diseases may cause hypo-albuminaemia means that the incidence of malnutrition may have been over-estimated.

Be that as it may, the time has come for a fresh approach to the nutritional assessment of surgical patients. It will come as no surprise to the journeyman surgeon that the best way of assessing surgical malnutrition is by clinical means. Recent research suggests that a detailed history and a proper physical examination can assess fairly accurately the *efficacy* and *appropriateness* of nutritional repletion. However, this must be something more than a global assessment by the operating surgeon from the end of the bed[2,3]. The key is to be able to estimate weight loss properly and assess its impact on physiological function. The surgeon must also be able to identify the causes of significant metabolic stress. It is not all that difficult to carry out a proper clinical assessment of nutritional status with an eye to these important facts. Weight loss of more than 10 per cent over the previous 3 months is important, and confirmation that this amount of weight has been lost can be obtained by palpating several skin folds and muscle bellies. The overall impact of the lost weight on physiological function is assessed from the history and by examination. The history must reveal clear evidence that there has been a significant change in the capacity for activity, or in any specific physiological function, over the same period as the loss of weight. On physical examination, muscular weakness is assessed by asking the patient to squeeze the examiner's hand to feel if there is impairment, taking into account his age, sex, and body habitus. Unhealed cuts or sores suggest impairment of wound healing, and metabolic stress can be said to be present when there are unequivocal signs of sepsis or recent injury. Finally, the patient is carefully observed for his activity level and endurance around the ward. Using these simple clinical techniques a decision can be made about whether the patient is nutritionally depleted (weight loss with physiological impairment) and/or metabolically stressed. Different forms of malnutrition can be identified, namely: nutritional depletion without stress, nutritional depletion with stress and no significant depletion but metabolic stress present[4]. With this clinical categorization, a fairly clear prediction can be made as to the likely efficacy of nutritional repletion. It has been shown recently that patients with no sign of stress, but who are depleted, will gain body protein with a 2-week course of intravenous nutrition; depleted patients with moderately severe surgical stress will have protein stores preserved but not increased by these means; and for those with major surgical stress, such as intensive care patients, intravenous nutrition is of supportive value only[5,6].

The appropriateness of nutritional repletion, particularly in the case of pre-operative patients, is the subject of considerable debate. Experienced surgeons know that weight loss does not appear to be an important risk factor for postoperative complications unless it is associated with clinically obvious impairment of physiological function. Preliminary studies at the University of Auckland suggested that patients who were physiologically impaired could be identified by a thorough clinical examination. A formal prospective trial was then commenced to determine whether clinical assessment of weight loss and physiological function was able to identify patients with objective evidence of abnormal body composition and function who were also at an increased risk of postoperative complications[7]. Of 101 patients

0007-1323/88/080729-02$3 00

awaiting gastrointestinal surgery, 42 had weight loss greater than 10 per cent and also had clear evidence of physiological dysfunction. These patients had significantly more postoperative complications and a significantly longer hospital stay than the other patients, whether or not weight had been lost. Thus, it does appear that weight loss is a basic indicator of surgical risk providing it is associated with clinically obvious organ dysfunction.

Although a short course of nutritional repletion has been shown to increase body protein stores and improve some aspects of organ function in depleted non-stressed patients, it remains to be seen whether this will result in fewer postoperative complications and/or a shorter hospital stay. Until that is known a simple clinical protocol should be used. Marked weight loss associated with clinically obvious physiological impairment places the patient at a disadvantage and, providing he/she is not stressed, it can be anticipated that nutritional repletion will be accompanied by protein gain and functional improvement. If such a patient faces a long and complicated operation then a short period of nutritional repletion seems to make clinical common sense.

G. L. Hill

Department of Surgery
University of Auckland
New Zealand

1. McLaren DS. A fresh look at protein-energy malnutrition in the hospitalized patient. *Nutrition* 1988; 4. 1–6.
2. Baker JP, Detsky AS, Whitwell J, Langer B, Jeejeebhoy KN. A comparison of the predictive value of nutritional assessment techniques.. *Human Nutr Clin Nutr* 1982; 36: 233–41.
3. Pettigrew RA, Hill GL. Indicators of surgical risk and clinical judgment. *Br J Surg* 1986, 73, 47–51
4. Sheldon GF, Way LW. Surgical Metabolism and Nutrition. In Way LW, ed. *Current Surgical Diagnosis and Treatment*. Los Altos: Lange Medical Publications, 1985: 149.
5. Hill GL. Body composition research at the university of Auckland—some implications for modern surgical practice *Aust NZ J Surg* 1988; 58: 13–21.
6. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients *J Trauma* 1987, 27: 262–6.
7. Windsor JA, Hill GL. Weight loss with physiological impairment—basic indicator of surgical risk. *Ann Surg* 1988; 207: 290–6

Br. J. Surg. 1988, Vol. 75, August, 731–732

Acute surgical disease and scoring systems in daily surgical practice

In the past two decades, surgeons have begun to realize the value of predictive indicators of outcome in severe disease. The Glasgow Coma Scale is well entrenched in the daily practice of all those concerned in the care of head injury, while Child's grading system remains of unquestionable value in the assessment of patients with liver disease. On the other hand, some scoring systems such as those designed specifically for trauma, burns, surgical sepsis and acute pancreatitis are applied only in a few centres. Two trends are apparent in the current literature: the multiplication of 'personal scoring systems' in such conditions as upper gastrointestinal bleeding[1], perforated duodenal ulcer[2] and choledocholithiasis[3]; and 'personal modifications' of an already existing scoring system. Overwhelmed by the increasing number of scoring systems appearing in the literature, the general surgeon may ask: why should a scoring system be used; what benefits might be derived for the surgical patient; and which system (if any) should be used in a given situation?

The scoring of acute disease has three main functions. Firstly, to alert the clinician to the presence of severe disease; secondly, to help in the comparison of severity of illness within and between cohorts of patients; and lastly, to allow the selection of patients for trial of new forms of treatment.

A 'poor' score on admission may alert the surgeon to the presence of severe disease which is associated with an increased risk of intervention and a high probability of poor outcome. The use of a scoring system facilitates communication between the surgeon and other specialists. It is easier for the anaesthetist to understand the necessity for intensive intra-operative organ support and postoperative admission to an intensive care unit in a patient whose score indicates the presence of a grave disease.

A scoring system may prove a powerful tool in clinical research. Obviously, the most direct way of assessing the value of a new treatment is by a prospective, randomized, controlled trial. However, because of methodological and ethical considerations such studies are not always possible. The acceptance and use of one scoring system by all who care for the acutely ill patient would allow uniform reporting and increase the value of retrospective or uncontrolled studies. Furthermore, a scoring system would reflect the comparability of patients within a prospective trial; this is especially important if the trial includes a small number of patients.

Scoring of all acutely ill patients could assist the surgeon in the evaluation of the quality of care provided by his team. Lessons can be learned from the deaths and the survivals considered 'unexpected' on the basis of their scores. For example an elderly patient with a perforated viscus who presents with a 'favourable' score should survive the insult of both the disease and its surgical treatment. If he died, shortcomings in his management may be better identified and measures can be taken for their future prevention. A scoring system may also aid in the choice of an operation in the individual patient. For example, a definitive operation for perforated duodenal ulcer might be indicated in the patient with a 'favourable' score on admission, whereas simple closure might be preferred in a patient whose score indicates a compromised general condition. In such instances the scoring system might usefully supplement clinical judgment.

To achieve these goals clinicians would be best advised to use one language and adopt one score. Ideally, the score selected should be applicable to most acute diseases because the busy clinician is unlikely to use multiple scoring systems. Furthermore, an ideal score should be easy to master and use and its component parameters should be known soon after admission.

Which parameters should be taken into account by the ideal scoring system? Five main factors determine the outcome of an acute disease, namely: the type of the disease; its severity; the patient's age; his prior health status; and the treatment given. If the influence of any given therapy is to be assessed, the score should be determined before treatment is commenced. Obviously, the subsequent determinations of the score during therapy may evaluate the patient's progress and response to treatment. Which end points should be sought to evaluate the usefulness of a particular scoring system? Criteria such as the period of hospital stay, admission to an intensive care unit, and length and type of treatment given are influenced by the availability of facilities and by differences in management policy between individual centres or clinicians. Criteria

0007-1323/88/080731-02$3 00

such as presence of organ failure, which depends in part on factors already used in the scoring system, may not be appropriate. Thus, it seems that death or survival remain the best end points in the assessment of any scoring system.

An example of a scoring system used increasingly is the APACHE II system[4]. Disease severity is estimated by the use of 12 'physiological' values easily derived from the clinical assessment of the patient and from simple biochemical parameters. Age and previous health status are taken into account. The predictive power of APACHE II has been validated and it has been used in many acutely ill patients admitted to intensive care units with common surgical and medical diseases[4]. Others have found APACHE II to be useful in predicting outcome in intra-abdominal infection[5,6] and acute pancreatitis[7]. However, further prospective studies are needed to assess the applicability of APACHE II in other acute abdominal emergencies before its use can be recommended on a large scale.

Although the original APACHE II system was not developed as a basis for treatment decisions in individual patients, data from carefully described groups of patients can be used cautiously in decision-making. For example, the knowledge that none of 24 patients with APACHE II scores greater than 40 survived septicaemia[4] may assist in the decision to adopt non-operative management in the patient with a perforated viscus presenting with a score of 45.

As pointed out, regardless of the number of patients studied to validate a scoring system, prognostic estimates remain estimates. Decisions concerning the treatment of the individual patient will always require sound clinical judgement in combination with the interpretation of objective data and the wishes of the patient and his family. None the less, measurement of the severity of the acute disease with a unified scoring system may be helpful.

M. Schein

Department of Surgery
Medical School
2193 Parktown
Johannesburg
South Africa

1 Clason AE, Macleod DAD, Elton RA Clinical factors in the prediction of further haemorrhage or mortality in acute upper gastrointestinal haermorrhage. *Br J Surg* 1986; **73**: 985–7.

2. Boey J, Choi SKY, Alagaratnam TT, Poon A. Risk stratification in perforated duodenal ulcers. *Ann Surg* 1987; **205**. 22–6.

3. Neoptolemos JP, Davidson DE, Shaw DE, Lloyd D, Carr-Locke D, Fossard DP. Study of common bile duct exploration and endoscopic sphincterotomy in a consecutive series of 438 patients. *Br J Surg* 1987; **74**. 916–21

4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29.

5. Ponting GA, Sim AJW, Dudley HAF. Comparison of the local and systemic effects of sepsis in predicting survival *Br J Surg* 1987, **74**: 750–2.

6. Dellinger EP, Wertz MJ, Meakins JL *et al.* Surgical infection stratification system for intra-abdominal infection *Arch Surg* 1985, **120**: 21–9.

7. Larvin M, McMahon MJ. Serial objective measurements of severity in acute pancreatitis. *Gut* 1987, **28**: A369.

Br. J. Surg. 1988, Vol. 75, August,
733–736

Abdominal aortic aneurysm

P. R. S. Thomas and
R. D. Stewart

Whipps Cross Hospital,
Leytonstone, London, UK
Correspondence to:
Mr P. R S. Thomas, Department
of Surgery, St James' Hospital,
London SW12 8HX, UK

Between 1981 and 1986, 282 cases of abdominal aortic aneurysm were diagnosed in Waltham Forest. Rupture had occurred in 183, 15 underwent urgent operation for intact aneurysm, and 84 had elective surgery. The incidence of rupture increased from 13 to 21 per 100 000 population during the 6-year period. Operative mortality for patients with rupture was 54·7 per cent, but the mortality overall was 81·4 per cent. In 59 per cent of patients with rupture no operation was performed, and 35·0 per cent of all deaths occurred in the community. The mortality for rupture in women was significantly higher than in men, although the operative mortality was comparable. Fifty patients (27 per cent) were found to have attended hospital within 2 years of rupture and many had documented evidence of an aneurysm. One-third of all patients admitted with rupture were undiagnosed. This study complements the previous small number of community studies and suggests that the incidence of rupture is increasing nationally particularly in women, where the mortality was exceptionally high. Early elective surgery is the key to the problem and improved clinical awareness could save many patients without elaborate and expensive programmes to screen the 'at risk' population.

Keywords: Abdominal aortic aneurysm, rupture, mortality

Advances in anaesthesia and vascular surgery have reduced the mortality for elective repair of abdominal aortic aneurysm (AAA) to less than 5 per cent[1,2], but the mortality for patients admitted to hospital with ruptured aneurysm remains greater than 50 per cent[3]. These figures, based on hospital data, underestimate the overall mortality which in post-mortem studies has been reported to be over 80 per cent[4], and as high as 94 per cent in a large Swedish study[5]. A programme to screen 'high risk' groups has been proposed as part of an aggressive policy to find and treat patients in the community with asymptomatic AAA[6]. In practice such a programme would be beyond the present resources available for acute health care.

This study was undertaken to examine the apparently high incidence of patients admitted to our hospital with ruptured AAA. We found that many of these patients had had their aneurysm previously documented or had recently attended hospital for other reasons. We decided to review all patients with ruptured AAA in detail to assess whether an internal screening programme could be developed to improve diagnosis and thereby the rate of referral for elective surgery. It was hoped that our interest in the study would alert colleagues to the prevalence of aortic aneurysms, the survival benefit gained from elective surgery[7], and also reduce delay in referral of urgent cases We felt that our data would complement the few community studies available and would provide a basis for comparison of a more active policy towards elective repair.

Patients and methods

Whipps Cross Hospital is an 850-bedded district general hospital serving the Waltham Forest Health Authority This encompasses four districts of East London, with a total resident population of 215 800[8] Of these, 34 700 were over 65 and 16 100 over 75 years of age Although the study was commenced in late 1983, it includes all patients treated in the 6-year period between January 1981 and December 1986, and who were resident in Waltham Forest Attempts were made to trace patients' records through the following sources: hospital admission and discharge data, casualty, theatre and intensive care unit records, the register of deaths, and post-mortem reports Information was also obtained from the Coroner's Office to ensure that those patients who died in the community were also included.

Patients were allocated to one of three groups

Group 1. Ruptured—where blood was found outside the aortic lumen, either at the time of surgery or at post mortem.

Group 2. Acute—patients presenting with sufficient symptoms or signs to merit urgent exploration within 24 h of admission, but where subsequent operation showed there had been no leakage of blood outside the aortic lumen.

Group 3. Elective—patients admitted non-urgently, without signs or symptoms of rupture for elective surgery

Surgery was performed in all cases by one of four consultant surgeons or a senior registrar Two of the consultants have a special interest in vascular surgery and performed most of the elective surgery Patients with aneurysm of the thoracic aorta, aortic dissection, acute thrombosis, and one young male with Marfan's syndrome were excluded from the study.

Results

A total of 282 patients with AAA were studied retrospectively. There were 183 patients with rupture (136 male, 47 female) of whom 75 underwent surgery (*Tables 1* and *2*); 15 patients were acute requiring urgent surgery for intact aneurysm (12 male, 3 female); and a further 84 patients (76 male, 8 female) were admitted for elective repair.

In group 1, 34 patients survived (mortality 81·4 per cent), while in group 2 there were 13 survivors (mortality 13·3 per cent). In group 3, 77 patients survived elective surgery (mortality 8·3 per cent).

Table 1 *Mortality for patients with abdominal aortic aneurysm according to mode of presentation*

	Male	Female	Total
Ruptured			
Number	136	47	183
Survivors (mortality)	31 (77·2%)	3 (93·6%)	34 (81·4%)
Acute			
Number	12	3	15
Survivors (mortality)	11 (8·3%)	2 (33·3%)	13 (13·3%)
Elective			
Number	76	8	84
Survivors (mortality)	70 (7·9%)	7 (12·5%)	77 (8·3%)

0007-1323/88/080733–04$3 00 © 1988 Butterworth & Co (Publishers) Ltd

Table 2 *Annual survival and mortality for patients presenting with aortic aneurysm in Waltham Forest*

	Year of presentation						
	1981	1982	1983	1984	1985	1986	Total
Ruptured							
Died	24	20	26	21	22	36	149
Survived	4	3	2	7	9	9	34
Total	28	23	28	28	31	45	183
Acute							
Died	0	0	0	0	1	1	2
Survived	2	4	1	2	4	0	13
Total	2	4	1	2	5	1	15
Elective							
Died	1	3	1	0	1	1	7
Survived	6	8	10	8	22	23	77
Total	7	11	11	8	23	24	84

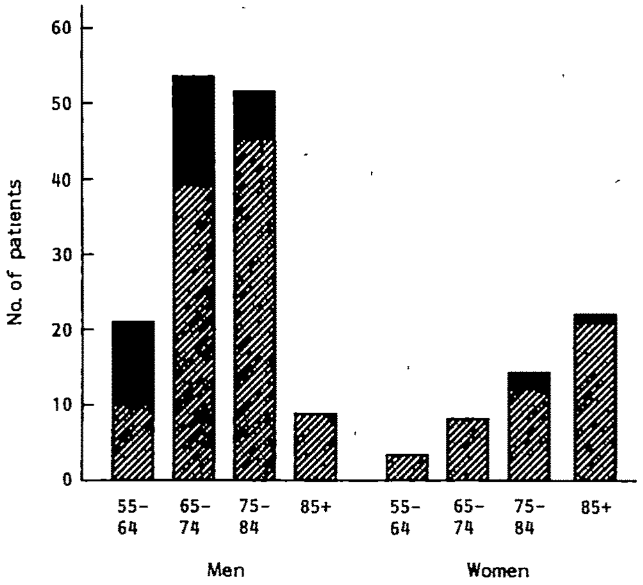


Figure 1 *Mortality for patients presenting with ruptured aneurysm according to age and sex.* ■, *Survivors,* ▨, *deaths*

This study examined an apparently well-defined population with all patients resident within Waltham Forest, although it is possible that some patients could have been referred elsewhere for treatment. The overall incidence of rupture rose from 13·0 per 100000 in 1981 to 20·9 per 100000 in 1986. The mean incidence of rupture in men and women over 55 years was 138 and 80 per 100000 per annum, and increased to 173 and 105 per 100000 respectively in the over-65 age groups.

Mortality for patients presenting with rupture was analysed according to age and sex (*Figure 1*). There was a significant difference between age of presentation in men (mean 73·4, s.d. 8·0 years) and women (mean 81·4, s.d. 9·4 years, $P<0{\cdot}001$). The overall male:female ratio for ruptured aneurysms was 2·9:1. This ratio changed dramatically with age, ranging from 7:1 in the 55–75 age group to 3·7:1 between the ages of 75 and 85 and actually reversing to 1:2·3 in patients over 85 years of age. Women had a significantly higher mortality than men (93·6 per cent compared with 77·2 per cent, $\chi^2=6{\cdot}22$, $P=0{\cdot}013$) with no survivors under the age of 75 years (*Figure 1*), although there was no difference in survival between men and women who underwent surgery (*Table 3*).

Figure 2 shows the cumulative mortality for rupture according to the place of death. Sixty patients died without reaching hospital with a further four patients declared dead on arrival in casualty, representing 35·0 per cent of all ruptured cases. Twenty patients (10·9 per cent) died in the casualty department and a further twenty-four patients (13·1 per cent) died on a ward without surgery. Thus out of 183 patients with rupture, 108 died without undergoing surgery (59·0 per cent). Of the remaining 75 cases, 34 survived, 26 died within the operating theatre and 15 died within 30 days of surgery, giving an operative mortality of 54·7 per cent.

There were few data available for analysis of the patients who died outside hospital but they showed a decreased incidence in the overall male:female ratio (1·46:1) and were on average older (men 3·6 years, women 7·7 years) than patients alive on admission to hospital. The correct diagnosis was made in only 5 of the 20 patients who died in casualty (25 per cent), of whom 2 were declined surgery on account of age (both over 85 years) and 3 died during attempted resuscitation. Eleven of the other patients were profoundly shocked and died within 20 min of arrival. Of the 24 patients dying on the wards, 15 were considered unfit for surgery: 11 were rejected on grounds of age alone (mean 89·6 years, range 80–102), 2 had severe ischaemic heart disease, one had chronic airways obstruction (on home oxygen) and one patient had disseminated malignancy. The remaining 9 patients were undiagnosed at the time of death.

Table 3 shows survival related to age for those patients who reached hospital alive and those who underwent surgery compared with overall survival. It is predictable that optimal survival was in the 55–64 years age group and declined with age. Only 8·1 per cent of patients with rupture over the age of 75 survived.

In an attempt to discover whether, with improved hospital screening and awareness, it would be possible to identify a greater number of patients with aneurysm, records were

Table 3 *Percentage survival according to sex and age for patients reaching hospital and theatre compared with overall survival*

	Survival of patients reaching hospital (%)	Survival of patients reaching theatre (%)	Overall survival (%)
Sex			
Male	32·0	44·9	22·8
Female	15·0	50·0	6·4
All	28·0	45·3	18·6
Age			
55–64	50·0	73·3	45·8
65–74	30·4	41·2	22·6
75–84	22·2	34·8	12·1
85+	7·7	33 3	3·3

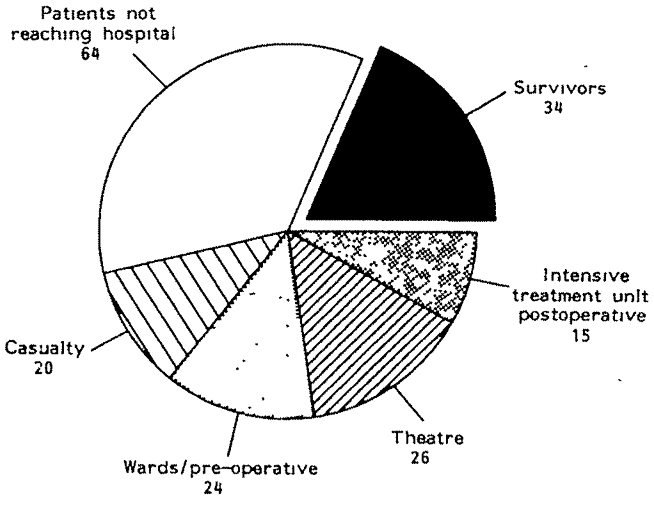


Figure 2 *Deaths and survivors in cases of rupture according to location*

analysed to determine how many patients had recently attended departments within the hospital. Of the 183 patients who presented with rupture, 50 (27·3 per cent) had been admitted to hospital within the last 2 years. In 18 cases aneurysm was undetected although 11 of these patients had presented with symptoms such as back pain which might have been attributable to their aneurysm. In the remaining 32 cases aneurysm had been recorded but no further action taken for the following reasons: unfit for surgery (5 cases); age (8 cases, mean age 86 years); incidental finding by radiologist (3 cases); and in 11 cases it was recorded as a clinical finding with no subsequent referral. Five patients under the vascular clinic had been lost to follow-up or their aneurysm had ruptured between appointments.

Previous studies have found hypertension to be an important risk factor[9] and analysis of our records showed that 34·6 per cent of patients were taking medication for hypertension at the time of rupture although only a few of these were under hospital supervision (this compared with 48·8 per cent of those admitted for elective repair who were known to be hypertensive). Other studies[3] have shown that the incidence of rupture may be subject to seasonal variation but we found no statistical correlation between the incidence of rupture and time of the year.

Discussion

The mortality for patients presenting with ruptured AAA without surgery approaches 100 per cent[10] but only half of those undergoing surgery will survive[10,11,12]. This is the 'tip of the iceberg'[13], and the true mortality may be as high as 94 per cent when deaths in the community are included[5]. Mortality for elective surgery even in the elderly varies from 2 to 10 per cent[10,14]. Life expectancy after repair compares favourably with matched population controls[15] although survival after repair in patients over 80 years of age may be less than 3 years[16].

Overall mortality for elective surgery was 8·3 per cent, but decreased in the second half of the study to 3·6 per cent (*Table 2*), and included one patient who died of a myocardial infarction during induction of anaesthesia. The mortality for those patients whose aneurysm had ruptured was 81·4 per cent which is similar to that found from combined post-mortem and hospital studies[4]. This takes account of the considerable number of deaths occurring outside hospital, with a mortality of 54·7 per cent for patients reaching theatre, which again is similar to comparable series[17]. *Figure 2* shows how misleading data for hospital mortality can be in obscuring the true and lethal nature of aneurysmal disease.

Our original suspicion that there was an unusually high incidence of ruptured aneurysms presenting to our hospital has been confirmed with an annual incidence higher than previously reported[3]. Aneurysm rupture is usually considered to be a disease affecting males[14] but a recent study[3] and our data show that the increasing incidence in men is exceeded by an even greater increase in women. Turk[18] suggested that aneurysmal disease progresses more rapidly in women which might explain the lower rate of detection. *Figure 1* shows that mortality was also higher in women (93·6 per cent overall), with no female survivors under 75 years of age.

At present, health care is not directed towards screening the at-risk population in Waltham Forest so we examined the possible benefits of improving detection within the hospital population. We found that 27 per cent of patients presenting with rupture had either attended hospital within the last 2 years or their aneurysm had been documented in some form. We also found that a number of patients presenting with rupture had been inappropriately referred or remained undiagnosed until an untimely death. Of the 119 patients who reached hospital alive, 20 died in casualty with a ruptured aneurysm diagnosed in only five cases. Fifty per cent were alive for 30 min or more in the department and with prompt diagnosis and immediate transfer to an operating theatre some of these patients might have survived. Previous reports have highlighted the problems of diagnosis[19,20]. In our series 33 of the 99 patients (mean age 72·5 years) were admitted from casualty with an incorrect diagnosis leading to a delay that may have contributed to subsequent mortality. At Whipps Cross Hospital computer-aided diagnosis is used as an adjunct to the diagnosis of patients presenting with acute abdomen but at the present time this programme has no provision for selecting cases of aneurysm. In a busy department, with relatively inexperienced junior staff, aneurysms may not immediately be detected and valuable time may be lost on unnecessary investigations. Once an aneurysm is suspected, immediate action is required to avoid the fatal delay. We would propose that aneurysm be included as a possible diagnosis if such programmes are to be used.

This study provides new evidence that AAA is an increasing national problem. Rupture in females carried a significantly higher mortality, only partly attributable to the later age of presentation. The elimination of rupture in Waltham Forest would involve a screening programme to select out asymptomatic cases from the population. If we applied Collin's equation[6] there would be a fivefold increase in elective surgery just to eliminate rupture in men and this would add an estimated one million pounds to the acute care budget. The adoption of such a policy on a national scale would require considerable extra capital expenditure and provision for more surgeons with vascular training. Short of adopting such an adventurous programme designed to bring aneurysmal rupture to the point of extinction, we suggest that there are many patients who with current resources could be selected for elective surgery with the prospect of a successful outcome.

Acknowledgements

We would like to thank Mr M. C. Pietroni, Mr P. A. Thomas, Mr J. M. Wellwood and Mr D. N. Offen for allowing us to study their patients, and also their secretaries for helping with the retrieval of patients' records.

References

1. Soreide O, Lillestol J, Christensen O *et al.* Abdominal aortic aneurysms: survival analysis of 434 patients. *Surgery* 1982; **91**: 188–93.
2. Crawford ES, Saleh SA, Babb JW, Glaeser DH *et al.* Infrarenal abdominal aortic aneurysms. Factors influencing survival after operation performed for a 25-year period. *Ann Surg* 1981; **193**: 699–709.
3. Castleden WM, Mercer JC, and members of the West Australian Vascular Service. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
4. Ingolby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986; **73**: 551–3.
5. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. *Br J Surg* 1986; **73**: 101–3.
6. Collin J. Screening for abdominal aortic aneurysms. *Br J Surg* 1985; **72**: 851–2.
7. Hicks GL, Eastland MW, Deweese JA, May AG, Rob CG. Survival improvement following aortic aneurysm resection. *Ann Surg* 1975; **181**: 863–9.
8. Office of Population and Census Studies. London, 1986.
9. Foster JH, Bolasnny BL, Gobbel WG Jr, Scott HW Jr. Comparative study of elective resection and expectant treatment of abdominal aortic aneurysm. *Surg Gynecol Obstet* 1969; **129**: 1–9.
10. Harris KA, Amelia FM, Lally M *et al.* Abdominal aortic aneurysm resection in patients more than 80 years old. *Surg Gynecol Obstet* 1986; **162**: 536–8.
11. Butler MJ, Chant ADB, Webster JHH. Ruptured abdominal aortic aneurysms. *Br J Surg* 1978; **65**: 839–41.
12. Makin GS. Changing fashions in surgery of aortic aneurysms. *Ann R Coll Surg Engl* 1983; **65**: 308–10.

13. Armour RH. Survivors of ruptured abdominal aortic aneurysms; the iceberg's tip. *Br Med J* 1977; **ii**: 1055–7.
14. Gowland Hopkins NF. Abdominal aortic aneurysms. *Br Med J* 1987; **294**: 790–1.
15. Fielding JWL, Black J, Ashton F, Slaney G, Campbell DJ. Diagnosis and management of 528 abdominal aortic aneurysms. *Br Med J* 1981; **283**: 355–9.
16. Baker WH, Munns JR. Aneurysmectomy in the aged. *Arch Surg* 1975; **110**: 513–17.
17. Fielding JWL, Black J, Ashton F, Slaney G. Ruptured aortic aneurysms: postoperative complications and their aetiology. *Br J Surg* 1984; **71**: 487–91.
18. Turk KAD. The post-mortem incidence of abdominal aortic aneurysm. *Proc R Soc Med* 1965; **58**: 869–70.
19. McGregor JC. Unoperated ruptured abdominal aortic aneurysms: a retrospective clinicopathological study over a period of 10 years. *Br J Surg* 1976; **63**: 113–16.
20. Gardham JRC. Diagnosis not to be missed: abdominal aortic aneurysm. *Br J Hosp Med*. 1982; **28**: 40–7.

Paper accepted 29 March 1988

Surgical workshop

Br. J. Surg. 1988, Vol. 75, August, 736

Use of skin staples for fashioning colostomies

R. M. Antrum and J. J. Price

Bradford Royal Infirmary, Duckworth Lane, Bradford, West Yorkshire, UK
Correspondence to: Mr J. J. Price

Automatic staplers are becoming popular for skin closure. Since 1986, we have adopted the use of an automatic skin stapler for fashioning 50 consecutive colostomies, with a complication rate of 2 per cent. Prior to this we sutured colostomies with catgut and in 136 consecutive cases have had a complication rate of 23·5 per cent (colon sloughing 8·1 per cent, colon retraction 13·2 per cent and colon necrosis 2·2 per cent).

Methods

The colon is exteriorized in the normal fashion for an end or loop colostomy. The exteriorized bowel is opened, approximated to adjacent skin with toothed dissecting forceps or Littlewood forceps, and secured with 12 staples, regularly placed around the circumference (*Figure 1*). The stapling is completed within 30 s. The staples are removed on the tenth day using a simple extracting device. The Proximate II stapler (Ethicon Ltd, Edinburgh, UK) was used throughout.

Results

Fifty consecutive stapled colostomies have been performed without major complication. Three patients developed stomal oedema (6 per cent) which resolved after removal of the staples on the tenth day. Only in one case was there any partial retraction from the skin edge (2 per cent).

Our stomatherapist commented that the staples were easier to remove than silk sutures.

Discussion

Although the complications documented in the conventionally sutured colostomies are not particularly serious they delay colostomy training and therefore the patient's discharge from hospital. The complications of colon retraction, sloughing and necrosis are probably explained by the tight sutures either cutting out or producing ischaemic bowel edges. These complications have not been a problem with skin staples which do not penetrate either the bowel wall or skin but merely approximate them without tension.

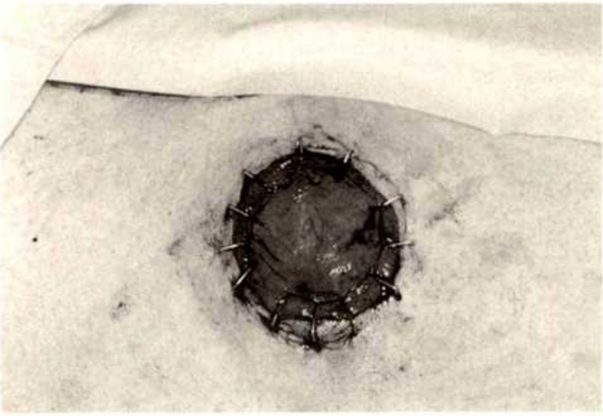


Figure 1 *The completed colostomy*

The cost of skin staplers (approximately £7.80 for a 25-staple dispenser and £8.50 for a 35-staple dispenser) initially appears somewhat prohibitive to their routine use. However, in a comparison of stapled and conventionally sutured laparotomy incisions Gatt *et al.*[1] demonstrated that a stapled skin incision cost approximately £0.50 more than a sutured one, but took only one-fifth of the time. The use of a skin stapler for colostomies is also not an extravagant luxury. For instance, the average laparotomy plus colostomy (e.g. Hartmann's procedure) would normally require 20 staples for the skin incision (Proximate TW25, cost £7.80). If a 35-staple dispenser (Proximate TW35, cost £8.50) is employed the remaining staples can be used for the colostomy; this would result in a cost of £0.70 for the colostomy which is considerably cheaper than using suture materials.

We would recommend the use of automatic staplers for colostomies, especially to surgeons who routinely use them for closing the skin. We feel that the procedure is simpler, quicker and the end result better than suturing the stoma.

Acknowledgements

We wish to thank our stomatherapist Mrs Mavis Watson for her help in the preparation of this paper.

References

1. Gatt D, Quick CRG, Owen-Smith MS. Staples for wound closure: a controlled trial. *Ann R Coll Surg Engl* 1985; **67**: 318–20.

Paper accepted 11 March 1988

0007–1323/88/080736–01$3.00

Br. J. Surg. 1988, Vol. 75, August,
737–740

Femorodistal vein bypass graft stenoses

M. J. Grigg,
A. N. Nicolaides and
J. H. N. Wolfe

Irvine Laboratory for Cardiovascular Investigation and Research and the Vascular Surgical Unit, St. Mary's Hospital Medical School, London W2, UK

Correspondence to:
Mr J. H. N. Wolfe, Vascular Unit,
St. Mary's Hospital, Praed Street,
London W2, UK

Eighty femorodistal in situ *vein bypass grafts have been evaluated at 3-monthly intervals clinically, with ankle:brachial pressure indices (ABI), by intravenous digital subtraction angiography (IV DSA) and by Duplex scanning. Five grafts (6 per cent) failed in the perioperative period. Nineteen (25 per cent) of the remaining 75 grafts subsequently developed stenoses on IV DSA during the first 12 months. All angiographic stenoses were detected by Duplex scanning using velocity ratio criteria before the development of symptoms or a measurable decline in ABI, i.e. while non-haemodynamically significant. This technique involves scanning the entire length of the graft but allows even minor stenoses to be detected and progression of stenoses can be determined. At a mean follow-up of 12 months (3–18 months), four (7 per cent) of the fifty-six grafts without stenoses occluded. Eight (42 per cent) of the nineteen stenosed grafts either occluded or developed symptoms. None of the occluded grafts in this series could be salvaged. Non-haemodynamically significant vein stenoses can be detected non-invasively, occur frequently and are associated with graft failure.*

Keywords: Vein graft stenosis, femorodistal bypass, Duplex scan

The failure of femoropopliteal and femorotibial vein bypass grafts continues to be a problem of considerable magnitude with reported failure rates of 20–50 per cent at 5 years[1–4]. Many of the failures occur within 2 years of operation. Brewster and colleagues reviewed 555 femoropopliteal grafts and reported that 79 per cent of failures occurred within 2 years; 65 per cent within the first year[5].

Szilagyi and associates studied the natural history of vein implants, identified graft stenoses and emphasized their adverse effects on long-term graft patency[6]. The incidence of vein graft stenoses has subsequently been reported to be 11–33 per cent[7–9], with 75 per cent of these appearing within the first postoperative year[10].

The detection and correction of vein graft stenoses before graft failure appears to be worthwhile. Whittemore and colleagues[11] reported a 5-year patency of 85 per cent for stenotic lesions repaired before graft thrombosis compared with only 37 per cent if secondary repair was undertaken. Bandyk and associates have reported primary patency rates at 3 years of 48 per cent for femoropopliteal grafts and 58 per cent for femorotibial grafts which were improved to 89 per cent and 80 per cent by vigilant postoperative surveillance and graft revision[4].

In the past, graft stenoses have usually been detected by the development of symptoms or by a fall in ankle pressures, i.e. relatively severe lesions producing a decline in graft flow. Non-haemodynamically significant lesions are more difficult to detect. We have previously employed intravenous digital subtraction angiography (IV DSA)[12] but this technique is demanding of both staff and patients. In addition, the haemodynamic relevance of an anatomical observation can only be inferred.

This study has been undertaken to develop a simple, accurate and non-invasive method for the detection of vein graft stenoses and to determine if non-haemodynamically significant lesions should be repaired. Previous authors have concentrated on haemodynamically significant stenoses and have had difficulty in identifying the non-haemodynamically significant lesion.

Patients and methods

Eighty femorodistal *in situ* vein bypass grafts performed in 74 patients were studied at 3-monthly intervals with: (1) clinical evaluation to elicit the development of symptoms or a change in distal pulse status; (2) ankle:brachial pressure indices before and after a standard exercise (1 min on a treadmill at 4 km/h with 10° elevation[13]); (3) IV DSA and (4) Duplex scanning of grafts. The indications for operation and the type of grafts performed are shown in *Table 1*.

All grafts entered in the follow-up study were considered to be satisfactory at the completion of operation, having been objectively assessed with operative arteriography and intra-operative Doppler.

Duplex scanning

The entire length of each graft was studied with a 7·5 MHz probe (Diasonics 300DRF). The angle between the pulsed Doppler beam and the graft was continuously calculated allowing conversions of the Doppler frequency information to velocity. Stenoses were defined by an increase in velocity of 50 per cent or more within a 2 cm length of graft (*see Figure 1*) i.e. $V_2:V_1 > 3:2$ where V_2 is the peak velocity at any point in the graft and V_1 is the peak velocity at any other point within 2 cm.

This approach is applicable to grafts which are devoid of branches. Flow at any point in the graft is the same as the flow at any other point. Because flow is the product of cross-sectional area and velocity, any reduction in cross-sectional area entails a compensatory increase in velocity. Cross-sectional area is dependent upon the square of the radius. Therefore, relative reductions in diameter are reflected by even larger changes in velocity (*see Figure 1*) so that even minor stenoses can be detected.

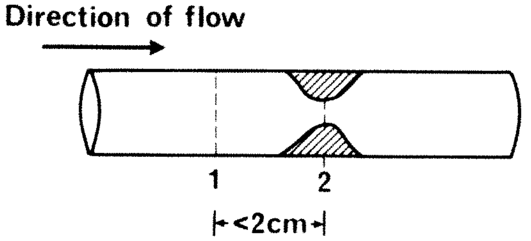
Study design

The presence or absence of stenotic lesion in grafts was determined by IV DSA. Duplex scanning was performed on all grafts independently and without knowledge of the result of the angiogram. Stenoses were subdivided into two groups: (1) 'haemodynamically significant' if there was a clinical deterioration, i.e. the development of symptoms in the presence of a patent graft, and/or a change in the ankle:brachial pressure index (ABI) of more than 0·2; (2) 'non-haemodynamically significant' if

Table 1 *Indication for and type of femorodistal bypass graft*

Clinical indication	Femoropopliteal grafts ($n=31$)	Femorocrural grafts ($n=49$)
Claudication ($n=23$)	23	—
Rest pain ($n=27$)	4	23
Critical ischaemia ($n=30$)	4	26

This study was supported by a grant from Impra UK



Flow = Cross-sectional area x Velocity

$$\text{Flow}_1 = \text{Flow}_2$$

Assuming cross-sectional areas are circular

$$\pi r_1^2 v_1 = \pi r_2^2 v_2$$

$$\therefore v_2/v_1 = \frac{r_1^2}{r_2^2}$$

$$\therefore \text{A } v_2 : v_1 \text{ ratio} = 3:2$$

suggests ≈ 20% reduction in diameter

Figure 1 *As grafts are devoid of branches, flow at point 1 should be equal to flow at point 2. A* V_2:V_1 *ratio* >3:2 *suggests a stenosis* >20 *per cent where* V_2 *is the peak velocity at point 2 and* V_1 *is the peak velocity at point 1*

Table 2 *Patency of grafts in relation to graft stenoses*

	Patent *n* (%)	Occluded *n* (%)
No stenosis ($n = 56$)	52 (93)	4 (7)
Non-haemodynamically significant ($n = 14$)	11 (79)	3 (21)
Haemodynamically significant ($n = 5$)*	5 (100)	—

* All 5 grafts with haemodynamically significant stenosis were electively repaired before graft failure and remain patent

there were no such changes. It was considered necessary to correct haemodynamically significant lesions. Consequently, these grafts were removed from the study and electively repaired with either percutaneous transluminal angioplasty or surgery.

Results

Five grafts (6 per cent) failed in the perioperative period (i.e. < 30 days) and were excluded from further analysis. At a mean follow-up of 12 months (range 3–18 months), 68 of 75 grafts (91 per cent) are patent although 5 (7 per cent) have undergone a secondary procedure. The overall primary graft patency was 79 per cent and the secondary patency 85 per cent.

The patency of grafts in the three categories (no stenosis, non-haemodynamic stenosis, haemodynamically significant stenosis) are shown in *Table 2*. Fifty-six grafts (75 per cent) had normal IV DSAs throughout the study period. However, four grafts (7 per cent) in this group occluded without warning. In all four of these grafts, graft thrombectomy was considered to be inappropriate and re-explorations were not performed because of the time lapse before patient presentation. All four patients were troubled with claudication but not with rest pain.

In 19 grafts (25 per cent) a stenosis was detected. The times at which stenoses first became apparent are shown in *Figure 2*. Seventeen (89 per cent) of the nineteen stenoses were apparent within 6 months of operation. All stenoses were detected by Duplex scanning using velocity criteria and were subsequently confirmed by angiography. Seven stenoses were situated in relation to the proximal anastomosis, ten in the body of the graft and two in relation to the distal anastomosis.

All stenoses were detected before the development of symptoms or a change in ABI > 0·2. Five lesions progressed to become haemodynamically significant, all within 3 months of being first detected. These five grafts were successfully repaired before graft failure, four with surgery and one with percutaneous transluminal angioplasty (*Figure 3*).

Of the 14 vein grafts with stenoses which remained 'non-haemodynamically significant', 3 have occluded and could not be salvaged. The patients eventually underwent more distal femorotibial procedures using prosthetic conduits (6 mm externally supported polytetrafluoroethylene (PTFE) Impra) and one patient remains with claudication.

The V_2:V_1 ratios of the grafts with and without stenoses in relation to ABI and angiographic assessments are shown in *Figure 4*. Of 23 grafts 19 (83 per cent) with a V_2:V_1 ratio >3:2 were subsequently confirmed to have a stenosis (> 25 per cent) on angiography.

Discussion

This study confirms previous reports that vein graft stenoses occur frequently if the graft is scrutinized carefully. An incidence of 15–33 per cent has been reported with most stenoses developing in the first 12 months after operation[5–12]. However, previous studies have identified stenoses by a decline in ABI or the development of symptoms, i.e. only haemodynamically significant lesions have been detected. In this study, the incidence of such lesions was five (7 per cent) of seventy-five vein grafts. It should be noted that these five patients who developed symptoms had a tendency to attribute the onset of claudication to 'over-usage' of the limb. No patient considered their graft to be 'malfunctioning'. This observation has served to emphasize the importance of patient education.

The peak velocity measurements obtained by Duplex scanning identified all 19 vein graft stenoses visible on DSA. This technique requires that the entire length of the graft be scanned and interrogated with pulsed Doppler ultrasound. In the early part of the study, it became apparent that attempts at B-mode ultrasound visualization of stenotic lesions were unrewarding. We have previously shown that peak velocity can be measured reliably with an experimental error of 15 per cent[14]. This error is small in relation to the velocity changes that occur even in relation to minor stenoses. In this series, we defined a stenosis as being present if velocity increased by more than 50 per cent over a 2 cm length of graft. This change in velocity corresponds approximately to a 20 per cent reduction in luminal diameter. In contrast, Duplex-derived flow

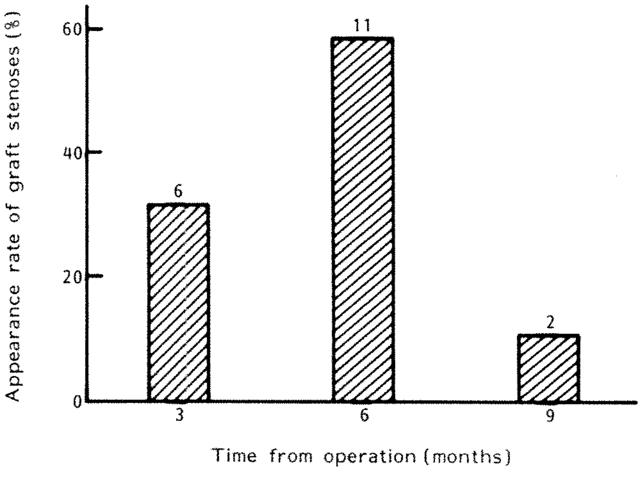


Figure 2 *The times at which vein graft stenoses were first detected. Of 19 stenoses, 17 (89 per cent) were detected in the first 6 months after operation*

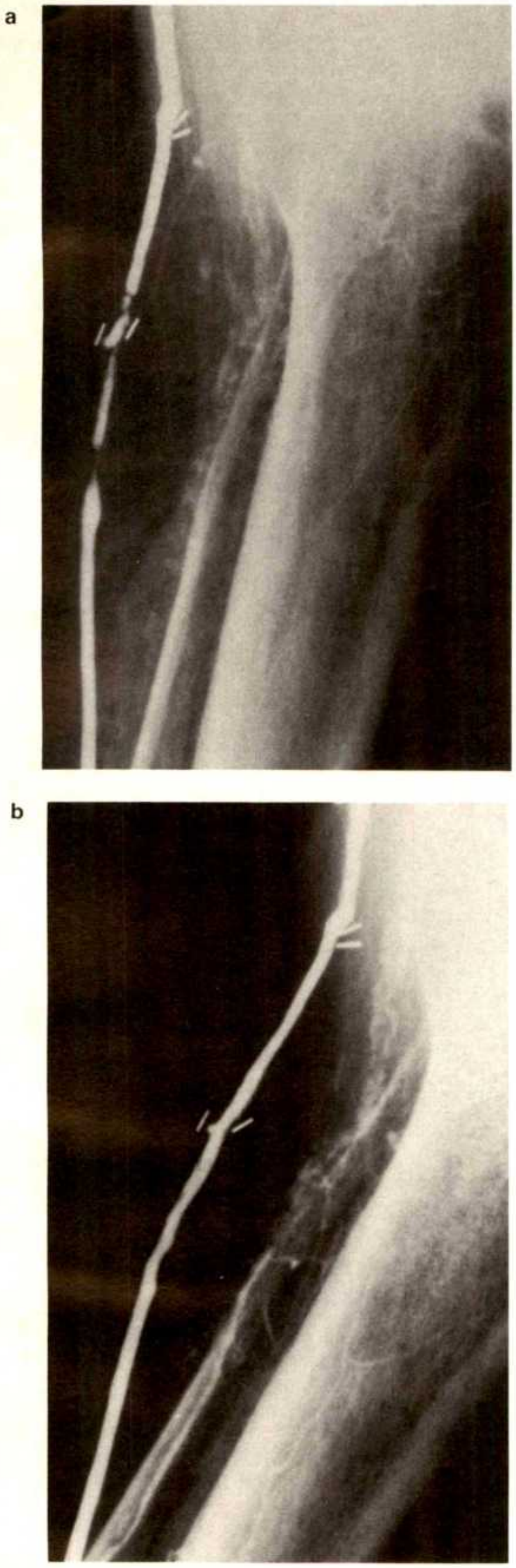


Figure 3 *Angiogram of a femorotibial vein graft* **a** *showing a haemodynamically significant stenosis below the level of the knee joint, and* **b** *following correction by percutaneous transluminal angioplasty*

measurements are not accurate[14], do not change until the stenosis is severe[15] and cannot localize a stenosis. Furthermore, they alter from day to day, even in normal grafts, owing to changes in cardiac output and peripheral resistance. The velocity criteria (V_2:V_1 ratio) should, on theoretical grounds, be independent of cardiac output and peripheral resistance. Therefore, an exercise stress test is not required and V_2:V_1 ratio obtained at one visit can be used as a comparison with V_2:V_1 ratios obtained on other days. Progression of stenoses can be assessed.

Vein graft stenoses occurring in the first year after operation have been recognized not only in femoropopliteal grafts (both *in situ* and reversed vein grafts[16]) but also in aortocoronary saphenous vein grafts[17,18], and histology reveals intimal or smooth muscle hyperplasia[6,17–19]. The reason for this development remains obscure and consequently a knowledge of how best to prevent the appearance of these lesions is limited. Prevention of endothelial trauma has been advocated but attempts at endothelial preservation have not convincingly reduced the incidence of later stenosis[20].

In this series, 7 of the 19 stenoses occurred in relation to the proximal anastomosis with relative sparing of the distal anastomosis (2 of 19). The reason for this is not clear, particularly as it is not our practice to clamp the proximal graft during operation. It is also interesting to note that, in this study, vein graft stenoses were singular with no incidence of multiple stenoses. This observation tends to counteract the proposition that grafts or patients have a generalized predisposition to smooth muscle hyperplasia, and suggests that local factors may be responsible.

It has been suggested that haemodynamically significant vein graft stenoses should be repaired when detected[4]. In this present study, all were satisfactorily repaired. Failure to intervene may have reduced graft patency from 85 per cent at 12 months to 79 per cent. Two methods of intervention are available: surgery, by means of vein patching or vein bypass, and percutaneous transluminal angioplasty. In general, we favour the former approach because of its proven success[5,7–11]. Percutaneous transluminal angioplasty of non-atheromatous lesions, i.e. vein graft stenoses, probably has inferior results to surgery[21] and Berkowitz[10] has reported a 2-year follow-up of 30

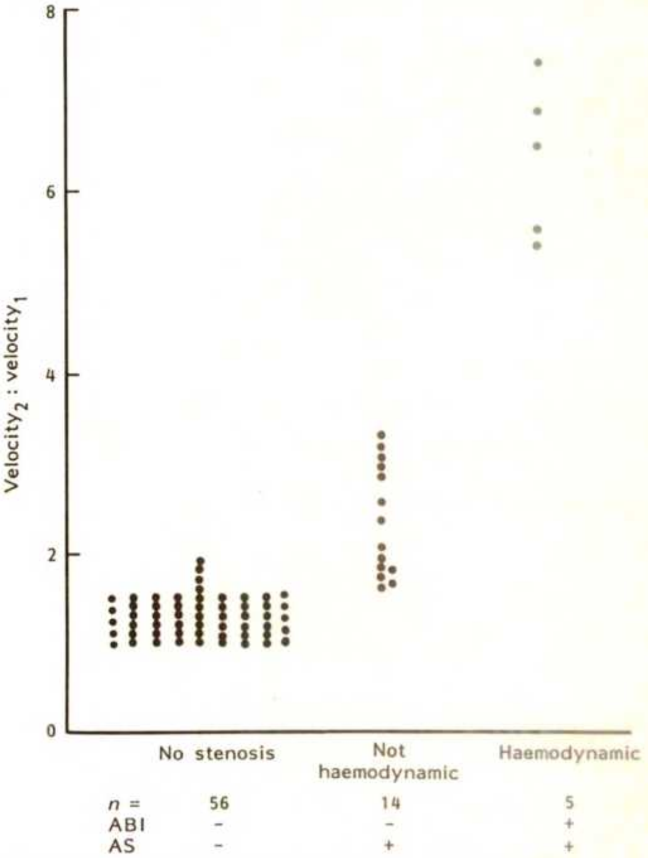


Figure 4 V_2:V_1 *ratios of 56 vein grafts with satisfactory ankle:brachial pressure indices (ABI) and angiography, of 14 vein grafts with an angiographic stenosis but no decline in ABI and of 5 vein graphs with an angiographic stenosis producing a fall in ABI >0·2. AS, angiographic assessment;* +, *with and* −, *without stenosis in relation to ABI and AS*

lesions treated with percutaneous transluminal angioplasty: 18 have remained patent, 6 occluded and 6 required surgery. Mannick's group suggests that surgery is more effective[21]. In our limited experience the use of a coronary balloon has been successful for appropriate lesions[22].

Four grafts occluded without warning or evidence of a stenosis. Thrombogenicity rather than mechanical factors could have contributed to the failure of these grafts, although it is possible that stenoses did in fact develop between assessments, as a surveillance interval of 3 months appears to be a significant time period in the development and progression of graft stenoses. In retrospect, the findings of this study support a 6-weekly surveillance programme for the first 6 months after operation (i.e. four visits). Thereafter the yield may be sufficiently low to allow follow-up of patients with clinical assessment and ankle:brachial pressure indices before and after exercise.

The early appearance of stenosis in this study compared with other studies employing ABI criteria may reflect the sensitivity of Duplex velocity criteria in detecting stenoses at a very early stage in their development.

Of the 19 vein grafts with stenoses, 8 (42 per cent) developed symptoms compared with only 4 of 56 (7 per cent) vein grafts without stenoses ($P<0{\cdot}001$). Of 14 grafts, 3 (21 per cent) with subclinical stenoses occluded without further warning and could not be salvaged. It is apparent that vein graft stenoses are not 'benign' lesions but, as 25 per cent of grafts develop a stenosis, repair of all stenoses would require a large number of secondary procedures. The improvement of 12-month patency rates which might be achieved does not, at present, justify the repair of all non-haemodynamic stenoses. Nevertheless, Duplex $V_2:V_1$ criteria offer the possibility of detecting the progression of stenoses. Although it may be possible to follow minor, stable stenoses, repair is probably indicated in those lesions demonstrating progression. This repair should be undertaken before stenoses become haemodynamically significant, because this is associated with sudden occlusion.

Acknowledgements

The authors would like to express their appreciation to the Cardiovascular Disease Educational and Research Trust (CDERT) for a grant to Mr M. Grigg, to Impra UK for a grant to Professor A. Nicolaides and Mr J. H. N. Wolfe without which the studies at St. Mary's would not have been possible; finally to Miss A. Taft for secretarial help.

References

1. Buda JA, Weber CJ, McAllister FF *et al.* Factors influencing patency of femoro-popliteal grafts. *Am J Surg* 1976; **132**: 8–12.
2. DeWeese JA, Rob CG. Autogeneous vein grafts ten years later. *Surgery* 1977; **82**: 775–84.
3. Maini BS, Mannick JA. The effect of arterial reconstruction on limb salvage. A ten year appraisal. *Arch Surg* 1978; **113**: 1297–1304.
4. Bandyk DF, Kasbnick HW, Stewart GW, Towne JB. Durability of the in-situ saphenous vein bypass. A comparison of primary and secondary patency. *J Vasc Surg* 1987; **5**: 256–8.
5. Brewster DC, La Salle AJ, Robison JG *et al.* Femoro-popliteal graft failures: clinical consequences and success of secondary reconstructions. *Arch Surg* 1983; **118**: 1043–7.
6. Szilagyi DE, Elliott JP, Hageman JH *et al.* Biological fate of autogeneous vein implants as arterial substitutes. *Ann Surg* 1973; **178**: 232–44.
7. Berkowitz HD, Hobbs CL, Crobers B *et al.* Value of routine vascular laboratory studies to identify vein graft stenosis. *Surgery* 1981; **90**: 971–9.
8. Sladen JG, Gilmour JL. Vein graft stenosis: characteristics and effect of treatment. *Am J Surg* 1981; **41**: 549–53.
9. Whitney DG, Kahn EM, Estes JW. Valvular occlusion of the arterialised saphenous vein. *Ann Surg* 1976; **42**: 879–86.
10. Berkowitz HD. Post-operative screening in peripheral arterial disease. In: Bernstein EF, ed. *Non-invasive Diagnostic Techniques in Vascular Disease*, 3rd ed. St Louis: C. V. Mosby Company, 1985: 632–8.
11. Whittemore AD, Clowes AW, Couch JNP. Secondary femoro-popliteal reconstruction. *Ann Surg* 1981; **193**: 35–42.
12. Wolfe JHN, Lea Thomas M, Jamieson CW, Browse NL, Burnand KG, Rutt DL. Early diagnosis of femorodistal graft stenoses. *Br J Surg* 1987; **74**: 268–70.
13. Laing SP, Greenhalgh RM. Standard exercise test to assess peripheral arterial disease. *Br Med J* 1980; **1**: 13–16.
14. Grigg MJ, Wolfe JHN, Tovar A, Nicolaides AN. The reliability of duplex derived haemodynamic measurements in the assessment of femoro-distal vein grafts. *Eur J Vasc Surg*, in press.
15. Strandness DE, Summer D. Physics of arterial blood flow. In: *Haemodynamics for Surgeons*. New York: Grune and Stratton, 1975: 73–95.
16. Harris PL, How TV, Jones DR. Prospectively randomized clinical trial to compare *in situ* and reversed saphenous vein grafts for femoropopliteal bypass. *Br J Surg* 1987; **74**: 252–5.
17. Bulkley BH, Hutchins GM. Accelerated 'atherosclerosis'. A morphological study of 97 saphenous vein coronary artery bypass grafts. *Circulation* 1987; **55**: 163–9.
18. Lawrie GM, Lie JT, Morris GC, Beazley ML. Vein graft patency and intimal proliferation after aorto-coronary bypass. *Am J Cardiol* 1976; **38**: 856–62.
19. Imparato AM, Bracco A, Kim GE, Zeff R. Intimal and neointimal fibrous proliferation causing failure of arterial reconstructions. *Surgery* 1972; **72**: 1007–17.
20. Combria RP, Megerman J, Abbott WM. Endothelial preservation in reversed and in-situ autogeneous vein grafts. *Ann Surg* 1985; **202**: 50–5.
21. Cohen JR, Mannick JA, Couch NP, Whittemore AD. Recognition and management of impending vein graft failure. *Arch Surg* 1986; **121**: 758–9.
22. McPherson S, Wolfe JHN. Femoro-distal graft failure: is our follow-up adequate? *Int Angiol* 1986; **5**: 281–7.

Paper accepted 10 April 1988

Br. J. Surg. 1988, Vol. 75, August, 741–742

Human gastric perfusion: evidence for non-uniformity of blood flow

P. I. M. Allen, I. Chesner*, K. Wheatley and M. Goldman

*Departments of Surgery and *Medicine, University of Birmingham, UK*

Correspondence to:
Mr M. Goldman, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST, UK

Post-mortem injection studies have demonstrated marked differences in the course and distribution of arterioles in the stomach, but evidence of differential perfusion in man is lacking. Using the non-invasive laser Doppler technique, we studied 38 patients referred for gastroscopy for dyspeptic symptoms. Flux measurements were made at nine sites: distal oesophagus, cardia, mid-body and antrum on lesser and greater curves, and pre- and post-pylorus. In all cases the stomach was macroscopically normal. Flux in the proximal stomach was significantly greater than that in the antrum, ($P<0{\cdot}001$, *Student's* t *test). This* in vivo *study demonstrates a flow gradient related to the previously demonstrated anatomical differences.*

Keywords: Gastric bloodflow, endoscopy, laser Doppler

Post-mortem injection studies of the human stomach have shown that the arterioles supplying the antrum and proximal duodenum are shorter and finer and form few anastomoses, compared with those supplying the rest of the stomach[1]. *In vivo* animal experiments to measure blood flow using dye dilution[2], hydrogen clearance[3] and radioactive microspheres[4] have given conflicting results. Furthermore, iodo-antipyridine clearance studies in humans showed marked discrepancies with previous animal results[5].

We have previously demonstrated that the non-invasive laser Doppler technique reliably reflects arterial flow when applied to the mucosal or serosal surface of the dog colon[6]. Briefly, coherent light from a helium–neon source is conducted via a flexible optical fibre to the tissue; some light is reflected unchanged from stationary cells, while some is reflected shifted in wavelength according to the Doppler principle, from moving cells. The instrument assesses red cell movement by analysing the interference pattern thus formed to give a measure of the movement (flux) beneath the probe. Since the red cells in the capillary circulation move in many different directions, the instrument does not give flow in ml/min; the voltage output of the instrument (V) is used as the arbitrary unit of flux. We report our experience of applying this method to study gastric perfusion in patients.

Patients and methods

Thirty-eight patients referred for diagnostic gastroscopy because of dyspeptic symptoms gave permission to make blood flow measurements during their examination.

All endoscopies were performed under diazepam sedation, by two experienced endoscopists. After a standard endoscopy, the laser Doppler probe was passed along the biopsy channel of the endoscope Readings were made at nine sites: distal oesophagus, cardia, mid-body and antrum on the lesser and greater curves, and pre- and post-pylorus, using the Periflux PF2 instrument (Perimed, Sweden), and the 20 Hz–4 kHz Doppler shift frequency range and 3 s flux time constant filter to eliminate the pulse cycle from the readings. In each position, the probe was advanced until satisfactory coupling was achieved between the probe and the mucosa, shown by the signal level indicator on the display panel remaining constantly green. This was usually achieved when the probe was approximately 1 mm above the surface of the mucosa. The probe is easily seen in the viewing field and can be accurately positioned just above the mucosa to give a rapid reading. Alterations in angle between probe and mucosa did not appear to affect the readings, but in most cases the probe was positioned vertically above the tissue. In each case the reading was recorded when a steady state was reached

Results were analysed using Student's *t* test

Results

In every case the stomach was macroscopically normal. Readings were completed in 3–5 min after the endoscopy. The coefficient of variation between patients for the readings at each site ranged from 27·2 to 95·8 per cent, but the overall mean coefficient of variation was $60 \pm 15{\cdot}2$ per cent.

Mean gastric flux in the stomach rose from a minimum of $44{\cdot}4 \pm 23{\cdot}3$ V (±s.d. arbitrary units of flow) in the prepyloric region to $74{\cdot}9 \pm 44{\cdot}8$ V on the lesser curve at the cardia (*Figure 1*). There was no significant difference between lesser and greater curve readings at any level in the stomach. Flux values on both lesser and greater curves at the level of the cardia and of the mid-body were significantly greater than those in the antrum ($P<0{\cdot}001$).

Discussion

Endoscopic measurements using the laser Doppler are simple to make. Satisfactory readings require a steady relationship between probe and the tissue and this is more easily achieved when the cable is fixed. In contrast to our previous experience using the probe held by hand[6] the support from the endoscopic biopsy channel enables the laser Doppler readings to be obtained quickly. We have found in earlier validation experiments that the value of the flux reading is not altered either by rotation of the probe around its own axis, or by angulation of the probe to the mucosa within a range of ±20° from the vertical. Other groups have reported similar findings in feline stomach within the range 60–120°[7]. We did not insert the

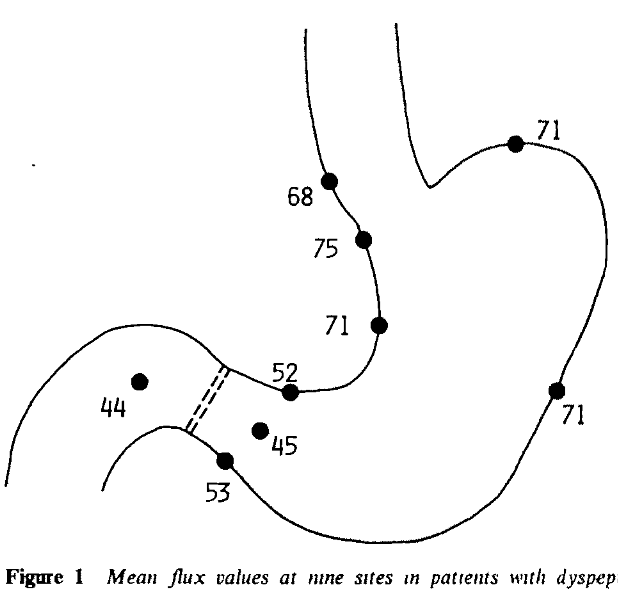


Figure 1 *Mean flux values at nine sites in patients with dyspeptic symptoms*

probe until the endoscope was in position in the stomach as the presence of the probe reduced the ability of the endoscope to aspirate gas and fluid. It is not clear what depth of tissue is assessed by this method. The manufacturer's literature[8] claims a depth of assessment of 1–1·5 mm; however, we found similar readings from both mucosal and serosal surfaces of the colon experimentally[6], and other groups have reported similar findings in the normal human stomach[7]. Our findings may relate to the overall stomach wall flow, rather than simply to mucosal flow, and may include flow in non-exchange vessels, e.g. arteriovenous anastomoses. Furthermore, since the stomach wall varies in thickness according to region it is possible that the contributions to the flux value from the mucosa, submucosa and muscularis vary from area to area.

The laser Doppler was originally developed for research in fluid mechanics[9] and used in industry to monitor flow of materials in manufacturing processes[10]. Its biological application to the measurement of blood flow has been compared experimentally with other microcirculation measurement techniques: microspheres[11], ^{133}xenon washout[12], and venous drop counters[7]. The laser Doppler appears to relate accurately and predictably to varying flow rates measured by these alternative techniques. We have compared laser Doppler with the electromagnetic measurement of variable arterial inflow in an isolated dog colon model and found a close correlation ($P<0\cdot001$, Student's *t* test). We also compared laser Doppler values with tissue oxygen tension at different arterial flow rates, and again showed good correlation ($0\cdot02>P>0\cdot01$)[6].

In this gastric study there was considerable variability in the readings obtained in different individuals. This may reflect different autonomic responses to the examination or true differences between individuals. We have recently examined the day-to-day variability in flux readings in patients undergoing regular surveillance endoscopy for oesophageal varices (as we did not feel it ethical to ask the patients undergoing a diagnostic endoscopy for dyspepsia to undergo a second endoscopy). In these patients, we found a coefficient of correlation of 0·510 ($0\cdot01>P>0\cdot001$, Student's *t* test). The interindividual variation in readings which we found may limit the diagnostic use of the instrument, but the trends within each individual do appear to give consistent results.

Human gastric blood flow has been studied in normal volunteers using iodo-antipyrine[13] and laser Doppler[7,14]. Our results demonstrating lower duodenal compared with gastric body flow agree with all three studies, although Kvernebo *et al.*[14] demonstrated a significant difference between lesser an greater curve flux, which we have failed to find.

Our finding of a significant blood flow gradient across th stomach supports the suggestion that peptic ulcers are localize to the antrum and duodenum, because of relative ischaemi which permits acid damage to the mucosal surface layer[15]. W are currently examining this possibility.

References

1. Barlow TE, Bentley FH, Walder DN Arteries, veins an arteriovenous anastomoses in the human stomach. *Surg Gynec Obstet* 1951; **93**: 657–71.
2. Bell PRF. Gastric arteriovenous shunts. *Scan J Gastroenter* 1967; 2: 59–67.
3. Semb BKH. Gastric flow measured with hydrogen clearanc technique. *Scand J Gastroenterol* 1979; **14**. 641–6.
4. Archibald LH, Moody FG, Simons M Measurement of gastri blood flow with radioactive microspheres. *J Appl Physiol* 197 **38**: 1051–6
5. Dugas MC, Wechsler RL. Validity of iodo-antipyrine clearanc for measuring gastrointestinal blood flow. *Am J Physiol* 198 **243**: G155–171
6. Allen PIM, Gourevitch D, Goldman M. A new technique t assess gastrointestinal blood flow. *Br J Surg* 1987, **74**: 1053–5
7. Ahn H. *Measurement of Gastrointestinal Blood Flow with Las Doppler Flowmetry* Linkoping University Medical Dissertatio 266. 1986.
8. *Periflux PF2 Users' Handbook*. Perimed; Sweden: 1985: 11.
9. Rudd MJ. The laser Doppler—a practical instrument. *Optic Technology* 1969; 1· 264–5
10. Botcherby SCL, Bartley-Denniss GA. *Optics Technology* 1969, 1 85–8.
11. Yeh Y, Cummins HZ. Localized fluid flow measurements with a He–Ne laser spectrometer. *Appl Phys Lett* 1964; **4**· 176–8.
12. Hellem S, Jacobsen LS, Nilsson GE, Lewis DH. Measurement microvascular blood flow in cancellous bone using laser Dopple flowmetry and ^{133}xenon clearance. *Int J Oral Surg* 1983, **12**: 165 77.
13. Wechsler RL, Dugas MC. Human GI mucosal blood flo measured by the iodo-antipyridine clearance techniqu *Gastroenterology* 1981, **84**: 1346.
14. Kvernebo K, Lunde OC, Stranden E, Larsen S Human gastri blood circulation evaluated by endoscopic laser Dopple flowmetry. *Scand J Gastroenterol* 1986; **21** 685–92
15. Piasecki C. The role of ischaemia in the initiation of peptic ulce *Ann R Coll Surg Engl* 1977; **59**. 476–8

Paper accepted 28 March 1988

Br. J. Surg. 1988, Vol. 75, August, 743–746

Reproducibility of reactive hyperaemia test in the measurement of peripheral arterial disease

F. G. R. Fowkes,
E. Housley*,
C. C. A. Macintyre†,
R. J. Prescott† and
C. V. Ruckley*

*Department of Community Medicine, University of Edinburgh, *Peripheral Vascular Clinic, Royal Infirmary of Edinburgh, and †Medical Statistics Unit, University of Edinburgh, UK*

Correspondence to:
Dr F. G. R. Fowkes, Department of Community Medicine, University of Edinburgh, Medical School, Teviot Place, Edinburgh EH8 9AG, UK

The reproducibility and sources of variation in ankle and brachial systolic pressures were determined for a reactive hyperaemia test used to assess peripheral arterial disease in the lower limbs. Thirty-six subjects had repeat measurements taken by four observers on two separate days using a Doppler probe and random zero sphygmomanometer. Ankle pressures were measured before and after 4 min of arterial occlusion above the knee. The 95 per cent confidence limits for a postocclusion reduction in pressure was approximately ±25 mmHg and for the postocclusion ankle–brachial ratio was ±20 per cent. The corresponding figures for the mean of four measurements taken by two observers on 2 days was approximately ±17 mmHg and ±13 per cent. In patients with vascular disease analysis of variance showed that the greatest sources of variation in the postocclusion ankle–brachial ratio were the 'biological' variations between subjects and between legs. But for postocclusion reductions in pressure, variability due to observers and repeat readings was as important as the 'biological' differences between subjects and legs. Thus, in respect of variability, the ratio may be a better parameter to detect differences between subjects.

Keywords: Arteriosclerosis obliterans, diagnosis, blood pressure determination, peripheral arterial disease

Despite the advent of innovative technological procedures for the assessment of peripheral arterial disease, the measurement of ankle systolic pressure using a Doppler probe is still the mainstay for diagnosis in clinical practice. In many patients with moderate disease, ankle pressures may be normal at rest but a reduction in pressure can occur after exercise or the temporary obstruction of blood flow inducing reactive hyperaemia.

In the reactive hyperaemia test, blood flow is occluded at the upper thigh or above the knee, and the ankle systolic pressure measured on releasing the obstruction. The systolic pressure in patients with peripheral arterial disease is reduced two to three times further and takes longer to return to pre-occlusion levels than in healthy subjects[1–4]. An occlusion time of 3 min has been shown to produce similar effects to that occurring after longer occlusion times[5,6]. Measuring the systolic pressure at between 15 and 30 s after the cuff has been released would appear to be the optimum time to distinguish between subjects with angiogram positive disease and controls[1,3].

Exercise tests have traditionally been used as a means of stressing the peripheral arterial system. But during recent years, the reactive hyperaemia test has been advocated by some clinicians because they believe it to be simpler, cheaper and quicker to perform[1–3,7] and the results show good correlation with exercise tests[2,3,8–10]. Furthermore, the test is less prone to patients affecting the degree of stress applied, particularly if they are old and have orthopaedic or neurological abnormalities. Also, the stress is applied when the patient is lying down and does not require any movement of the patient after the cessation of the stress with the possibility that the ankle blood pressure will be measured too late to detect the optimum difference from the resting state[2].

The usefulness of a test is however affected by its variability. In clinical practice and in research, particularly on large numbers of patients, it is often not feasible to take more than one set of measurements. The results of such measurements will vary depending on when and by whom they were taken. The extent of this variability needs to be known to determine how reliable one set of measurements is in reflecting the true situation in an individual patient and in affecting the results of research. The aim of this study was to determine the extent and sources of variation of a reactive hyperaemia test.

Patients and methods

The study was conducted on 36 subjects aged 40–74 years in the Peripheral Vascular Clinic, Royal Infirmary of Edinburgh. Twenty-four subjects with symptomatic peripheral arterial disease were selected from successive patients attending the clinic, patients were excluded if they had severe disease manifest by previous amputation, gangrene, or pain at rest. Twelve subjects were 'healthy' volunteers in that they did not give a history of intermittent claudication and their peripheral pulses were present, one of these volunteers was found subsequently to have disease (manifest by a low ankle–brachial systolic ratio), and was excluded from the analysis. Subjects were invited to attend the Peripheral Vascular Clinic on two afternoons approximately 2 weeks apart.

Four physiological measurement technicians were recruited specially to conduct the observations on the subjects. These four observers underwent intensive training in the Peripheral Vascular Clinic until it was considered on subjective grounds that they were suitably skilled at taking the measurements.

The examination of each subject took place in one of two identical rooms in the clinic. The temperature of the rooms was continually checked and kept at between 20 and 23°C. On arrival at the clinic the subject waited for at least 10 min in the waiting room, then entered the examination room, removed appropriate clothing, and rested on the examination couch for 10 min.

The right brachial systolic pressure was measured twice by an observer followed by the right ankle pressure (twice) and left ankle pressure (twice). Reactive hyperaemia was measured twice on each leg, but alternately between legs to allow each leg time to recover between measurements. Pressures in the arm and leg were measured using a random zero sphygmomanometer[11] and blood flow detected during deflation of the cuff by means of an auditory signal from a Doppler probe (Sonicaid BV 102R) placed over the brachial and posterior tibial arteries.

In the reactive hyperaemia test, blood flow was occluded above the knee using a pressure cuff inflated to 50 mm above systolic pressure for

0007-1323/88/080743-04$3.00 © 1988 Butterworth & Co (Publishers) Ltd

4 min. The measurement of ankle pressure started 15 s after releasing the occlusion, this timing was chosen for logistical reasons and because 15 s or longer has been used in other studies[1,3]. An electronic timer with auditory signal was used by each observer to control the timing. Ideally, brachial pressure should have been taken again during the reactive hyperaemia test, particularly at the time the postocclusion ankle pressure was measured, but this was not easily done Also our main interest in setting up the study was to measure the variability in reduction in ankle pressure, irrespective of changes in brachial pressure.

The subject then returned to the waiting room for approximately 40 min for some light refreshment (weak tea or juice and a biscuit). On re-entering the examination room he/she had 10 min rest followed by repetition of the tests by another observer. Two weeks later the subject had exactly the same routine except that the two observers were different from those present at the first visit.

A sequence was drawn up so that each observer took measurements on both first and second visits and on first and second sets of measurements within visits. The design ensured comparability between observers with respect to any possible period and 'carry over' effects. Subjects were allocated into the sequence based on their ability to attend appointment times at the clinic Data from each set of measurements were recorded on a standard form by each observer who was blind to measurements by previous observers.

The principal aim of the data analysis was to examine the different components of variance in the measurements. But, as there were four observers and only two observation periods per day, the design of the study was not wholly balanced, therefore the components of variance could not be estimated using standard analysis of variance techniques. A program designed for the analysis of such data was used (REML)[12] This was devised by Patterson and Thompson[13] and provides estimates and standard errors of the various components The components were estimated separately for the normal and diseased subjects.

The different sources of variation examined were those due to subjects (subject), bias of observers (observer) and systematic variations between the two days (day), those between sets of measurements on the same day (time), between sets of measurements on the two days (day x time), and differences between the two legs (leg). The following non-systematic variations were estimated: interaction between the subjects and observers (subject x observer) and subjects and days (subject x day), differences between a subject's left and right leg measurements (subject x leg), in the way observers measure different legs (subject x leg x observer), and in day-to-day differences between legs (subject x leg x day). The residual variation was due to differences in repeat readings by the same observer Observer variation in its usual sense is represented by the sum of the subject x leg x observer and subject x observer components.

The methods of calculating the difference between pre- and post-occlusion ankle pressures and postocclusion ankle–brachial ratios were based on the same measurements, either first or second, within each set of measurements

Table 1 *Reactive hyperaemia test· mean reductions in ankle systolic pressure and mean ankle–brachial ratios in diseased and normal subjects by observer, day and time*

		Postocclusion ankle systolic pressure (mmHg)		Postocclusion ankle–brachial ratio		Pre- minus post-occlusion ankle systolic pressure (mmHg)	
		Normal	Arterial disease	Normal	Arterial disease	Normal	Arterial disease
Observer	1	144·7	85·4	1·15	0·61	3·9	20·8
	2	144·3	92·0	1·16	0·62	6·0	16·4
	3	135·7	76·4	1·10	0·53	9·6	28·5
	4	135·4	84·2	1·11	0·60	6·6	17·6
Day	1	142·7	87·2	1·14	0·60	4·5	19·6
	2	137·5	81·8	1·12	0·58	8·5	22·1
Time	1	136·5	81·7	1·11	0·57	9·2	22·6
	2	143·6	87·3	1·15	0·60	3·9	19·2

Results

Mean differences in readings between observers, between the first and second visit (days) and between the first and second set of measurements on the same day (times) are shown in *Table 1*. In general, the differences between observers were greater than between days and times. *Figure 1*, for example, shows the distribution of the first measurement of the postocclusion ankle–brachial ratios by each observer on the left leg of each subject. In some subjects the range of ratios was considerable, for example, 0·7 to 1·1 in subject 24. Overall, postocclusion ankle–brachial ratios recorded by observer 3 were lower than those by other observers (*Table 1*) and this is confirmed in *Figure 1* in which the lowest recordings in 20 out of 35 patients were made by this observer. Mean postocclusion ankle pressures and ratios were higher on the first day than on the second and for the second set of measurements compared with the first

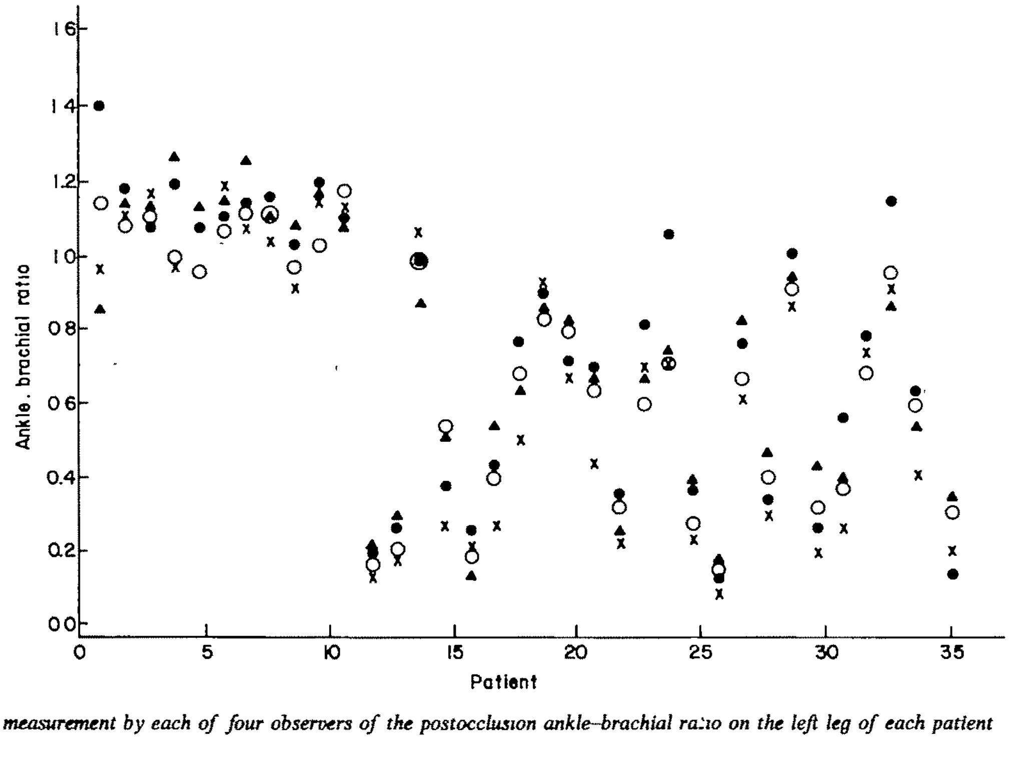


Figure 1 *First measurement by each of four observers of the postocclusion ankle–brachial ratio on the left leg of each patient*

Table 2 *Estimates of variance* and associated standard errors*

	Pre- minus postocclusion ankle systolic pressure		Postocclusion ankle–brachial ratio	
	Normal	Arterial disease	Normal	Arterial disease
Subject		84·5 (44·8)		320 (179)
Leg				10·4 (41·7)
Subject × leg		52·2 (25·1)		435 (133)
Time	15·5 (23·1)			
Subject × day	40·1 (18·9)	26·0 (17·9)	24·9 (14·9)	
Subject × leg × day	15·1 (10·5)			14·2 (10·3)
Observer (observer bias)		23·1 (21·5)		11·3 (10·5)
Subject × observer			18·6 (10·3)	14·5 (8·1)
Subject × leg × observer		95·4 (17·0)		27·5 (7·8)
Residual (repeat readings)	60·4 (9·2)	62·5 (6·4)	48·8 (10·6)	21·2 (2·2)

* Variance estimates < 10 are excluded from the table. Standard errors are given in parentheses

Table 3 *Ninety-five per cent confidence interval of reduction in ankle systolic pressures and postocclusion ankle–brachial ratio*

	Pre- minus postocclusion ankle systolic pressure (±mmHg)		Postocclusion ankle–brachial ratio (± %)	
	Normal	Arterial disease	Normal	Arterial disease
Mean of:				
One observer, one measurement	22·9	28·6	20·2	19·2
One observer, two repeat measurements	20·2	26·4	17·7	18·1
Two observers, one measurement each (same day)	20·0	21·6	16·4	15·0
Two observers, two measurements each (all on same day)	18·5	20·2	14·9	14·3
Two observers, two measurements each (one on one day and another on a different day)	15·3	18·9	12·8	13·1
Difference between two occasions:				
Same observer	31·9	26·9	25·2	18·1
Different observers	32·4	40·4	28·6	27·1

(*Table 1*). The pre-occlusion levels were very similar and hence the differences between days and times were reversed for the measurement of pre- minus postocclusion systolic pressures. As expected, diseased subjects had lower postocclusion pressures and ratios, and greater reductions in ankle pressure after occlusion than in normal subjects.

Table 2 shows the magnitude of the sources of variation among diseased and normal subjects. As expected there is considerable variation between diseased subjects (subject) and between the legs of diseased subjects (subject × leg). Also, noticeable variation in the measurement of left and right legs on the same subjects (subject × leg × observer) and systematic differences between observers (observer) occurred only among the diseased subjects. Observer variation as demonstrated by a combination of the (subject × observer) and (subject × leg × observer) components was greater in those with disease than in normal subjects, and in diseased subjects was greater for the pre- minus postocclusion pressure than the postocclusion ratio. Residual variation owing to differences in repeat readings by the same observer was present for all measurements.

The figures in *Table 2* have been used to estimate the precision likely to be associated with a measurement made under given conditions; these are shown in *Table 3*. Precision increased with the number of measurements when taken by different observers on different days. For example, in diseased subjects the 95 per cent confidence interval of a postocclusion reduction in ankle pressure was ±28·6 mmHg, and was ±18·9 mmHg for the average of four measurements owing to each of two observers taking one measurement on one day and another on a different day. The precision of the postocclusion reduction in pressure was slightly worse in diseased than normal subjects, but the precision of the ankle–brachial ratio was similar between the two groups. The confidence interval of the difference between two readings (*Table 3*) indicates the variability that can occur without a change in the subject's clinical condition; or conversely, a difference between two clinical readings greater than that stated in the table indicates that the subject's clinical condition is likely to have changed.

Discussion

The principal finding of this study is the considerable variability of the measurements associated with the reactive hyperaemia test. The 95 per cent confidence limits of one measurement of the postocclusion ankle–brachial ratio was approximately ±20 per cent and for the pre- minus postocclusion ankle pressure was approximately ±25 mmHg. This variability cannot be attributed to the quality of the observers or to the research method. The four observers had intensive training and were considered to be as good, if not better, than experienced medical staff in taking the measurements. All the tests were carried out under standard conditions: the environment and timing of the tests were strictly controlled. Use of the random zero sphygmomanometer decreased the risk of 'cheating' by the observers. Our results were comparable to those of Ouriel *et al.*[14] who found that when one observer carried out reactive hyperaemia tests on ten patients with intermittent claudication on five occasions over 30 days, 95 per cent of ankle–brachial ratio measurements on one individual fell within ±29·4 per cent of the mean value.

The main sources of variation were not entirely consistent for normal and diseased subjects and for the two reactive hyperaemia measurements (*Table 2*). In general, variations between different times on the same day (between the first and second set of measurements) contributed little to the overall variability, whereas variations between different days had a more substantial effect. Likewise, there was considerable variability between repeat readings. The variability attributable to the observers occurred more predominantly among the diseased subjects. The relatively large subject × leg × observer variation, for example, suggests that some observers had more difficulty measuring one leg than another in some subjects. This presumably occurred more commonly in those with disease because of greater difficulty in measuring arterial flow.

Although the variability of pressure measurements associated with the reactive hyperaemia test was considerable, the variations were only slightly greater than those occurring for resting pressures. Among diseased subjects the 95 per cent confidence intervals for one measurement of the ankle–brachial ratio at rest was ±16·9 per cent and during reactive hyperaemia was ±19·2 per cent. Detailed analyses of the variability in resting pressures are published elsewhere[15]. Similar results have been obtained in other studies examining the variability of resting ankle systolic pressures[14,16–20]. Furthermore, the variability is comparable to that for brachial systolic pressures[21,22].

In comparison with the measurements of ankle pressures after exercise, the variability of the reactive hyperaemia test may be marginally better because it was found in one study[14] that 95 per cent of ankle–brachial ratios after exercise were within ±31·2 per cent of the mean value, whereas the corresponding figures for the reactive hyperaemia test was ±29·4 per cent of the mean value. This slight difference is not surprising because in the exercise test additional variability may be induced by the subject adapting to the test and also by the difficulties in moving the subject from the exercise treadmill to the couch.

What are the implications of these findings for clinical practice and research? The variability is such that care must be taken in the clinical interpretation of one measurement, particularly if that measurement is in the borderline range between normality and abnormality. As noted in *Table 3*, precision can be improved if repeat measurements are taken on different days and by different observers In monitoring clinical progress in patients, it is equally important that a change in postocclusion ankle–brachial ratios between measurements of say ±15 per cent is not necessarily ascribed to a change in the patient's clinical condition. Variability is reduced if the same observer sees the patient at each visit (*Table 3*). These comments also hold true for small clinical studies, but for many large scale epidemiological studies it is important that the variability within subjects from whatever cause is not sufficiently large to upset any variations between subjects. In the patients with vascular disease whom we examined, the variation between subjects (and legs) in postocclusion ankle–brachial ratios was the largest source of variation, but the same did not hold true for differences in ankle pressures before and after occlusion (*Table 2*). Thus, in respect of variability, the ratio may well be a better measurement to use to pick up differences between subjects.

Acknowledgements

We thank Margaret Apps, Elizabeth Cawood, Eileen Kerracher and Felicity Smith for taking the measurements. This study was supported by a grant from The British Heart Foundation.

References

1. Johnson WC. Doppler ankle pressure and reactive hyperaemia in the diagnosis of arterial insufficiency. *J Surg Res* 1975; **18**: 177–80.
2. Baker JD. Post stress Doppler ankle pressures. *Arch Surg* 1978; **113**: 1171–3
3. Hummel BW, Hummel BA, Mowbry A. *et al.* Reactive hyperaemia vs treadmill exercise testing in arterial disease. *Arch Surg* 1978, **113**· 95–8.
4. Verhagen PF, deJong TJ, Van Vroomhoven Th J. Ankle pressure changes during reactive hyperaemia in peripheral arterial disease. *Vasa* 1983; **12**: 29–34
5. Gundersen J. Standardised multisegmental measurements of blood pressure for quantitative evaluation of the circulation in the limbs. *Scan J Clin Lab Invest* 1973; **31**(Suppl 128): 111–15
6. Dedichen H, Myre HO. Reactive hyperaemia of the human lower limb *Acta Clin Scand* 1975; **141**. 517–21.
7. Bernstein EF, Fronek A Current status of noninvasive tests in the diagnosis of peripheral arterial disease. *Surg Clin North Am* 1982; **62**: 473–87.
8. Mahler F, Koen L, Jahnasen KH, Bernstein EG, Fronek A. Post-occlusive and post-exercise flow velocity and ankle pressures in normal and marathon runners. *Angiology* 1976; **27**: 721–8.
9. Fox MJ, Tripolitis A, Kirby S, Jamieson CW. A comparison of a reactive hyperaemia test with a standard exercise test in the evaluation of peripheral arterial disease *Br J Surg* 1977, **64**: 290 (Abstract)
10. Keagy BA, Pharr WF, Thomas D, Bowes DE. Comparison of reactive hyperaemia and treadmill tests in the evaluation of peripheral vascular disease *Am J Surg* 1981; **142**: 158–61
11. Wright BM, Dore CF A random-zero sphygmomanometer. *Lancet* 1970, i: 337–8
12. Robinson DL Estimation and use of variance components *Statistician* 1987; **36**: 3–14.
13. Patterson HD, Thompson R. Maximum likelihood estimation of components of variance. *Proceedings of 8th International Biometric Conference* 1975: 197–207
14. Ouriel K, McDonnell AE, Metz CE, Zarins CK A critical evaluation of stress testing in the diagnosis of peripheral vascular disease. *Surgery* 1982; **91**: 686–93.
15. Fowkes FGR, Housley E, Macintyre CCA, Prescott RJ, Ruckley CV Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. *J Epidem Comm Health* (in press).
16. Carter SA. Indirect systolic pressures and pulse waves in arterial occlusive disease of the lower extremities *Circulation* 1968, **37**: 624–38.
17. Gruntzig A, Schlumpf M. The validity and reliability of post stenotic blood pressure meaasurement by Doppler ultrasonic sphygmomanometry. *Vasa* 1974, 3 65–71.
18. Baker JD, Dix D. Variability of Doppler ankle pressures with arterial occlusive disease: an evaluation of ankle index and brachial–ankle pressure gradient. *Surgery* 1981; **89**: 134–7
19. Schroll M, Munck O Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population study of 60 year old men and women. *J Chron Dis* 1981, **34**. 261–9.
20. Osmundson PJ, O'Fallon M, Clements IP *et al.* Reproducibility of noninvasive test of peripheral occlusive arterial disease. *J Vasc Surg* 1985; **2**· 26–41.
21. Armitage P, Fox W, Rose GA, Tinker CM. The variability of measurements of casual blood pressure II. Survey experience. *Clin Sci* 1966, **30**: 337–44.
22. Gordon T, Sorlie P, Kannel WB. Problems in the assessment of blood pressure: The Framingham Study *Int J Epidem* 1976; **5**· 327–34.

Paper accepted 11 February 1988

Br. J. Surg. 1988, Vol. 75, August, 747–750

Endoscopic sclerotherapy in the treatment of gastric varices

Of 309 patients with portal hypertension, gastric varices were found in 48 (16 per cent). While the majority (88 per cent) of the patients had gastric varices in association with oesophageal varices, 6 (12 per cent) patients had 'isolated' gastric varices. Gastric varices were seen significantly ($P < 0{\cdot}01$) *more often with grade 4 than with grade 3 varices. In 11 (28 per cent) of the 40 patients who completed sclerotherapy for oesophageal varices, gastric varices disappeared concurrently on eradication of oesophageal varices or during the following 6 months. Of the initial five patients with gastric varices who received direct intravariceal injections, four rebled; this technique was therefore replaced by combination (paravariceal + intravariceal) gastric variceal sclerotherapy. Emergency combination sclerotherapy successfully controlled bleeding from gastric varices in six of the eight treated patients. Thirty-two patients entered a programme of elective combination gastric variceal sclerotherapy. Variceal obliteration was achieved in 12 cases (38 per cent) and reduction in size was noted in another 7 patients (22 per cent) after a minimum of four courses. There were 11 (23 per cent) deaths, 8 due to uncontrolled bleeding from gastric varices and 3 due to hepatic coma. The other complications of gastric variceal sclerotherapy were minor and included retrosternal pain, fever and dysphagia. It is concluded that gastric varices often coexist with large oesophageal varices. If they persist for 6 months after eradication of oesophageal varices, a combination of paravariceal and intravariceal sclerotherapy should be attempted for their obliteration.*

Keywords: Endoscopic sclerotherapy, gastric varices, portal hypertension

S. K. Sarin, G. Sachdev, R. Nanda, S. P. Misra and S. L. Broor

Department of Gastroenterology, G. B Pant Hospital, New Delhi, India

Correspondence to: Dr S K Sarin, Associate Professor, Department of Gastroenterology, G. B. Pant Hospital, New Delhi-110002, India

Endoscopic sclerotherapy has become the treatment of choice for the obliteration of oesophageal varices[1–4] and is also recommended for the control of active variceal bleeding[5,6]. Gastric varices are sometimes associated with oesophageal varices in patients with portal hypertension. Although bleeding from gastric varices is less frequent, it is difficult to diagnose and control[7,8]. The role of endoscopic sclerotherapy in the treatment of gastric varices has not been adequately evaluated so far; furthermore, the fate of co-existing gastric varices after eradication of oesophageal varices is not clearly known. In this communication we present our experience of managing gastric varices with endoscopic sclerotherapy.

Patients and methods

Patients

Of the 309 patients who underwent sclerotherapy in our unit between February 1983 and November 1986, 48 were diagnosed as having gastric varices with or without accompanying oesophageal varices. There were 31 men and 17 women with a mean age of 35·2 ± s.d. 17·4 years. Gastric varices were attributable to cirrhosis of the liver in 24 patients, to non-cirrhotic portal fibrosis (NCPF) in 14 and to extrahepatic portal vein obstruction in 10 patients. Six patients had 'isolated' gastric varices, that is, without any associated oesophageal varices. Three of these six patients had extrahepatic portal vein obstruction, two had a block at the splenic hilum as demonstrated by splenoportovenography and one had thrombosis of the splenic vein secondary to chronic pancreatitis and pseudocyst of the pancreas. Two other patients with 'isolated' gastric varices had cirrhosis of the liver and one patient had NCPF. The severity of liver disease was graded on the basis of Child's criteria. 31 patients belonged to Child's A, 8 to Child's B and 9 to Child's C class of liver disease.

The diagnosis of gastric varices was made at endoscopy with the concurrence of two experienced endoscopists, when they found one or more distinct venous channels in the fundus and/or just below the gastro-oesophageal junction. During active variceal bleeding, if there was doubt regarding the diagnosis, the patient was turned on to his right side during endoscopy for proper evaluation of the fundus of the stomach. In the initial three patients, selective angiography and splenoportovenography were done to confirm the endoscopic diagnosis of gastric varices. Oesophageal varices were graded from 1 to 4 (Reference 9). When gastric varices were seen in association with oesophageal varices in patients undergoing sclerotherapy for the latter, the size and presence of gastric varices was recorded at each repeat sclerotherapy session. After eradication of oesophageal varices, these patients were examined endoscopically at monthly intervals to look for any recurrence of oesophageal varices or change in the status of gastric varices.

Technique of gastric variceal sclerotherapy

Sclerotherapy for gastric varices was started in August 1984 as an in-patient procedure using Olympus GIF Q, D3 or XP endoscopes, TEFLON® injector and absolute alcohol as a sclerosant, as described earlier for oesophageal variceal injection[3,10,11]. Initially a modified indigenous TEFLON injector with a needle length of 0·5 mm was used for placement in gastric varices. Subsequently, commercially available (Olympus NM—10L) TEFLON injectors were used. Gastric variceal sclerotherapy was done either by a straight end-on technique (i.e. by keeping the endoscope straight) or by retroflexion (i.e. by retroverting the endoscope at the incisura angularis) for better visualization of the fundus. The former technique was usually employed for gastric varices extending up to the cardia while the latter method was used for deep-seated fundal varices falling short of the gastro-oesophageal junction. In the initial five patients with gastric varices, only intravascular injections were given. All of the later patients received a combination of intravariceal and paravariceal injections. The combination technique involved initial injections of 0·5–1·0 ml absolute alcohol paravariceally at multiple sites raising blebs along the entire course of the gastric varix. On average, four injections (range 2–9) were given paravariceally

---

This work was presented in part at the meeting of the International Association for the Study of the Liver at Caracus in 1986, and was published in the proceedings of the meeting

TEFLON® *is a registered trademark of DuPont, UK*

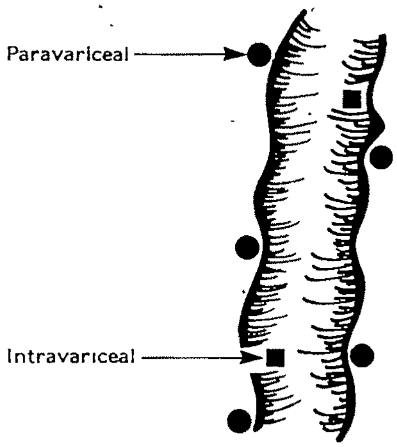


Figure 1 *Scheme of combination sclerotherapy First, paravariceal injections (●) are given 1–3 cm apart and then intravariceal injections (■) are placed on the side walls of the gastric varix*

Thereafter, the sclerosant was injected intravariceally into the gastric varix Usually 1–3 injections were given intravariceally to each gastric varix. Attainment of an area of about 0·5–1 0 cm of 'blanching' around the injection site was considered desirable for adequate sclerotherapy, as this criterion has been found to be useful in the sclerotherapy of oesophageal varices[10]. The most prominent point of the gastric varix was avoided during intravariceal injection and an attempt was made to give the injection on the side wall of the gastric varix (*Figure 1*) The endoscope was withdrawn only after complete haemostasis had been achieved and air and secretions were sucked out of the stomach to decompress it The patients were kept on nil orally for 4 h and were observed for the next week for any bleeding

Rebleeding was defined as any bleeding occurring from gastric varices before the next course of sclerotherapy. In the event of rebleeding, further sclerotherapy of gastric varices was attempted initially. If it failed, we resorted to balloon tamponade with only the gastric balloon inflated.

Statistical analysis was done using Student's t test and χ^2 test with Yates' correction, if appropriate

Results

Association with oesophageal varices

Forty-two (88 per cent) patients with gastric varices had associated oesophageal varices, and six (12 per cent) patients had 'isolated' gastric varices. Gastric varices were seen significantly ($P<0.01$) more often with grade 4 (60 per cent) than with grade 3 (31 per cent) oesophageal varices. None of the patients with grade 1 and only four (10 per cent) patients with grade 2 oesophageal varices had associated gastric varices. The frequency of gastric varices in patients with different aetiologies of portal hypertension did not differ significantly, being 14 per cent in those with cirrhosis, 18 per cent in those with NCPF, and 20 per cent in those with extrahepatic obstruction.

Course of gastric varices

Forty-two patients who had both oesophageal and gastric varices at the time of entry into the study, had undergone sclerotherapy only for oesophageal varices on either a 1- or 3-weekly schedule[7,10,11]. Two of these patients rebled from oesophageal varices after one and three courses of sclerotherapy respectively and succumbed (*Figure 2*). In 11 (28 per cent) of the 40 remaining patients, who were studied by monthly endoscopies, gastric varices disappeared or decreased either concurrently with the obliteration of oesophageal varices (in 7 patients) or between 1 and 6 months of follow-up after oesophageal variceal eradication in another 4 patients. Upper gastrointestinal bleeding occurred in two patients during the follow-up period. In both the patients, bleeding occurred at home. Endoscopy done at admission did not reveal the site of bleeding There was no evidence of gastritis.

Gastric variceal sclerotherapy

The indications for gastric variceal sclerotherapy were (1) bleeding from gastric varices; (2) persistence of gastric varices for 6 months or more after eradication of oesophageal varices; (3) recurrence as gastric varices after obliteration of oesophageal varices, and (4) presentation as bleeding from 'isolated' gastric varices (*Figures 2* and *3*).

Emergency sclerotherapy

Gastric varices were considered to be the cause of upper gastrointestinal bleeding in eight patients (although identification of active bleeding from the gastric varices was possible on eight occasions in seven of these patients). The exact cause of bleeding was identified only on five occasions· in three instances the bleeding was seen to be from a hole or a tear on the gastric varix, and on two occasions it was from an ulcer attributable to earlier sclerotherapy. Bleeding was successfully controlled by combined intravariceal and paravariceal injections in six of the eight episodes in six patients. In two patients with Child's B and C cirrhosis respectively, bleeding continued despite sclerotherapy. Balloon tamponade and intravenous vasopressin infusion also failed and both patients succumbed.

Elective sclerotherapy

In the first five of our patients, only intravariceal sclerotherapy was attempted (*Figure 3*). Immediate or delayed rebleeding was seen in four of these patients. In two patients, one with NCPF having 'isolated' gastric varices and another with Child's B cirrhosis, introduction of the needle into the gastric varix initiated immediate projectile and massive bleeding. The bleeding could only be controlled by balloon tamponade. In the other two cirrhotic patients with 'isolated' gastric varices, exsanguinating rebleeding occurred after 10 and 44 h respectively of successful intravariceal injection of gastric varices and both patients succumbed

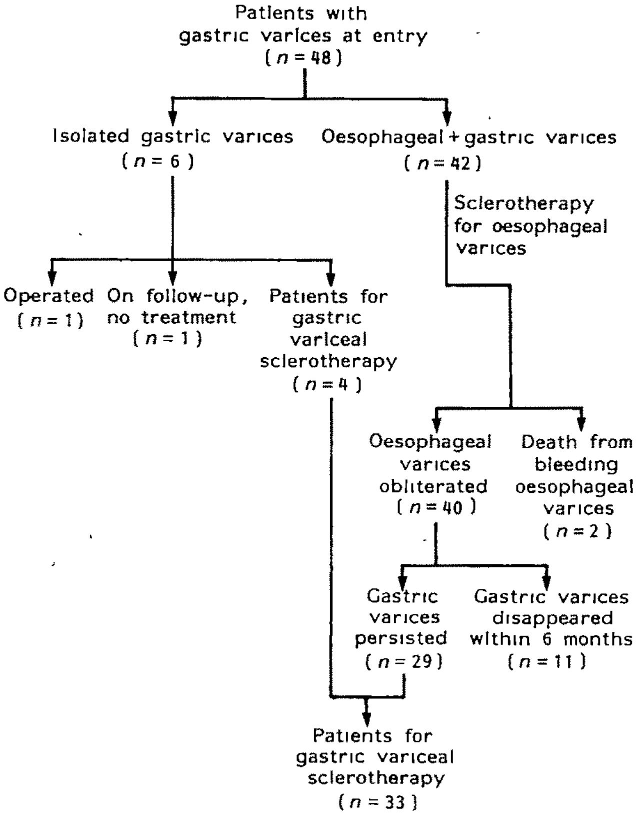

Patients with gastric varices at entry (n = 48)
Isolated gastric varices (n = 6)
Oesophageal + gastric varices (n = 42)
Sclerotherapy for oesophageal varices
Operated (n = 1)
On follow-up, no treatment (n = 1)
Patients for gastric variceal sclerotherapy (n = 4)
Oesophageal varices obliterated (n = 40)
Death from bleeding oesophageal varices (n = 2)
Gastric varices persisted (n = 29)
Gastric varices disappeared within 6 months (n = 11)
Patients for gastric variceal sclerotherapy (n = 33)

Figure 2 *Course of patients with gastric varices*

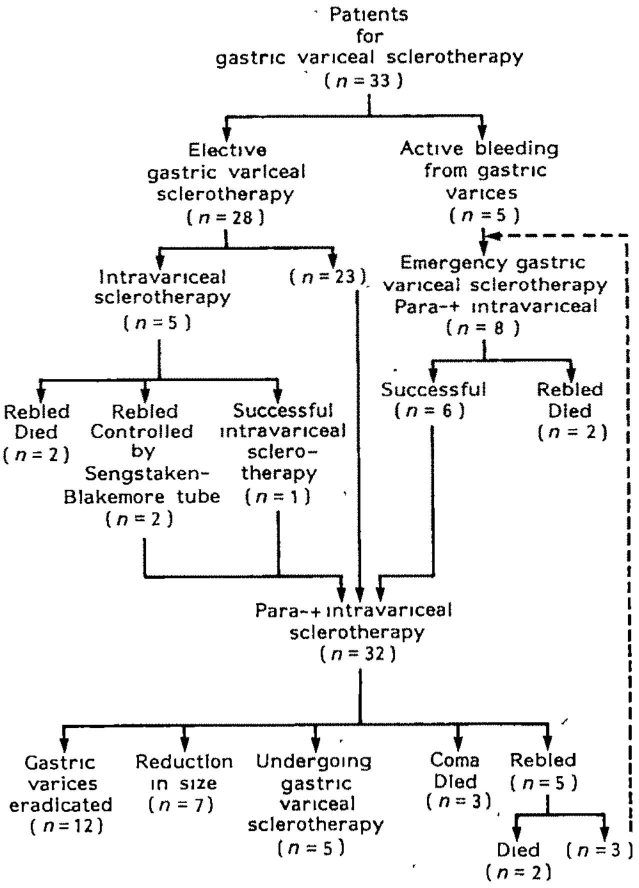

Patients for gastric variceal sclerotherapy (n = 33)
Elective gastric variceal sclerotherapy (n = 28)
Active bleeding from gastric varices (n = 5)
Intravariceal sclerotherapy (n = 5)
(n = 23)
Emergency gastric variceal sclerotherapy Para-+ intravariceal (n = 8)
Rebled Died (n = 2)
Rebled Controlled by Sengstaken-Blakemore tube (n = 2)
Successful intravariceal sclerotherapy (n = 1)
Successful (n = 6)
Rebled Died (n = 2)
Para-+ intravariceal sclerotherapy (n = 32)
Gastric varices eradicated (n = 12)
Reduction in size (n = 7)
Undergoing gastric variceal sclerotherapy (n = 5)
Coma Died (n = 3)
Rebled (n = 5)
Died (n = 2)
(n = 3)

Figure 3 *Results of intravariceal and combination gastric variceal sclerotherapy*

Thirty-two patients underwent a combination of intravariceal and paravariceal sclerotherapy at 3-weekly intervals. Total obliteration of gastric varices was achieved in 12 (38 per cent) patients. In another seven (22 per cent) patients, an appreciable reduction in the size of the gastric varices was achieved, giving an overall response rate of 59 per cent. A minimum of four courses of therapy were required for obliteration of gastric varices. In the 19 patients in whom varices were obliterated or reduced in size, the mean number of sclerotherapy sessions was 5·3 (±s.d. 2·1) and the amount of alcohol required for sclerotherapy was 31·3 ± 11·8 ml. At each session the mean number of intravariceal injections was 2·3 ± 1·4 and of paravariceal injections was 4·7 ± 3·7.

Mortality

Eleven (23 per cent) patients died, eight because of uncontrolled bleeding or rebleeding and three because of coma (*Figures 2* and *3*). All of these patients had cirrhosis of the liver (Child's A, 1 patient; Child's B, 5 patients; Child's C, 5 patients).

Complications

Overall rebleeding from gastric varices was seen in 12 (36 per cent) patients. Rebleeding after emergency combination gastric variceal sclerotherapy was seen in two of the eight, and after elective sclerotherapy, in five of the thirty-two (16 per cent) patients. Other complications included: retrosternal pain (36 per cent), fever (28 per cent) and dysphagia (14 per cent). These complications were mild and transient (1–48 h). Ulcers over the gastric mucosa due to paravariceal injections were seen in 38 per cent of patients. No recurrence or increase in the size of oesophageal varices was seen during a follow-up of 9·7 ± 4·4 months in the 19 patients who had achieved eradication or reduction in the size of gastric varices.

Discussion

There is limited information available on the exact incidence of gastric varices in portal hypertension patients[12]. Detection of gastric varices in 48 (16 per cent) of our 309 patients indicates that they are not uncommon. In the only other report of about 500 patients with portal hypertension and liver cirrhosis, Paquet has indicated that gastric varices are present in as many as 60–70 per cent of cases[8]. The wide discrepancy between Paquet's observations and our data could be due in part to the fact that in his series the criteria for the diagnosis of gastric varices were not well documented. Gastric varices are intramural and subserosal structures, and are generally located at the cardia and fundus of the stomach, appearing as thickened undulating folds. It is well known that they can be mistaken for tumours at endoscopy and barium studies[13] and for pseudotumours at computed tomography[14,15]. The other possibility is that we might have recorded a lower incidence of gastric varices in our patients because they are drawn from a different patient population. However, this seems unlikely, since there was no significant difference in the incidence of gastric varices in patients with different aetiologies of portal hypertension.

Gastric varices were seen in association with oesophageal varices in the majority (88 per cent) of our cases and significantly more often in patients with large varices. Only six patients had 'isolated' gastric varices. In a patient with unexplained recurrent upper gastrointestinal bleeding, only a high index of suspicion and special efforts at endoscopy may reveal that bleeding is coming from an 'isolated' gastric varix.

There are no large follow-up studies available on patients with gastric varices. MacDougall *et al.*[16] have reported persistence of gastric varices after disappearance of oesophageal varices in two patients. On the contrary, Terblanche *et al.*[17] have described disappearance of gastric varices after sclerosis of distal oesophageal veins. Our policy of waiting for 6 months after oesophageal variceal obliteration had both advantages and disadvantages. Of the 11 patients whose gastric varices disappeared within 6 months of our eradicating oesophageal varices (*Figure 2*), only four of the patients lost their gastric varices during the follow-up period while in seven they disappeared at the same time as the oesophageal varices. On the other hand, five of the thirty-three patients ultimately requiring gastric variceal sclerotherapy experienced bleeding from their gastric varices while in the 6-month observation period Probably the optimum period before starting gastric variceal sclerotherapy is less than 6 months after obliteration of oesophageal varices In any case, gastric varices should not be injected before oesophageal varices have been completely obliterated.

The exact mechanism of disappearance of gastric varices in some of the patients after obliteration of oesophageal varices is not clear. Contrast venographic studies have shown that in about 14 per cent of patients, the sclerosant injected into the oesophageal varices flows in a caudal direction, towards the gastric veins[18]. Recently, Terblanche and co-workers[19] have shown that large oesophageal varices characteristically arise from deep intrinsic veins of the oesophageal wall which communicate directly with gastric varices. It therefore seems possible that gastric varices are occluded in some patients by flow of the sclerosant from oesophageal to gastric varices.

Bleeding from gastric varices is managed in some centres by balloon tamponade followed by devascularization[8]. There is little information available on the use of endoscopic sclerotherapy in their management[1,2,4,8,20], and our initial experience of intravariceal sclerotherapy for the treatment of gastric varices was disappointing. Of the five patients in whom elective intravariceal sclerotherapy was attempted, significant rebleeding occurred in four and it was fatal in two cases. After these poor results, we abandoned intravariceal sclerotherapy of gastric varices. On the other hand, our technique of combined paravariceal and intravariceal injection was successful in controlling active bleeding from gastric varices in six of the eight patients in whom it was used. A minimum of four courses of sclerotherapy were found to be necessary for obliteration or achieving reduction in the size of gastric varices. As in the case of oesophageal varices[3], it seems likely that further courses of sclerotherapy would lead to gastric variceal obliteration in a larger number of patients. In a small anecdotal experience, Stray *et al*[21] had reported success following gastric paravariceal injection in three patients. Long-term follow-up of their patients with repeated sclerotherapy is, however, not available. In another study by Yassin *et al.*[22], obliteration of gastric variceal columns was achieved in six of the thirty-five (17 per cent) patients. The details of their patient population and technique are not available.

Rebleeding was the major complication after gastric variceal sclerotherapy and was seen in 36 per cent of our injected patients. The incidence of rebleeding was significantly higher after direct intravariceal injection (four of five patients) as compared with elective combination therapy (five of thirty-two patients). It is possible that the practice of first injecting the paravariceal areas may produce local ischaemia, which may help to reduce the chance of immediate rebleeding. Paravariceal injections are also likely to be helpful by initiating a fibro-inflammatory response in the submucosa. A few technical points need to be stressed: paravariceal injections should always precede intravariceal injections; in intravariceal injection of gastric varices the needle should be inserted in the side wall and not the apex of the varix, and blanching after intravariceal injection should be achieved. The only disadvantage of combination sclerotherapy is the high incidence of ulceration following paravariceal injection. These ulcers differ from oesophageal mucosal ulcers which are known to heal spontaneously in the majority of cases[23]. Gastric ulcers were seen in 38 per cent of patients and were identified as the cause of bleeding in two cases. In the study of Yassin *et al.*[22] rebleeding following injection was also seen in 37 per cent of patients, and, in the majority, it was from post-sclerotherapy ulcers or from non-variceal causes. Sucralfate, which has been shown to be promising in the healing of post-sclerotherapy oesophageal ulcers[24], may be of use in the treatment of ulceration following gastric variceal sclerotherapy[25].

References

1. Terblanche J, Bornman PC, Kahn D, Kirsch RE The management of acute variceal bleeding. In: Popper H, Schaffner F, eds. *Progress in Liver Diseases, Vol. VIII* Philadelphia: Grune and Stratton, 1986: 54–5
2. Williams R, Westaby D. Endoscopic sclerotherapy for oesophageal varices. *Dig Dis Sci* 1986; **31**. 108–21 (suppl.).
3. Sarin SK, Sachdev G, Nanda R, Vij JC, Anand BS. Endoscopic sclerotherapy using absolute alcohol. *Gut* 1985; **26**: 120–4.
4. Fleischer D. Endoscopic therapy of upper gastrointestinal bleeding in humans. *Gastroenterology* 1986; **90**: 217–34
5. Sarin SK, Nanda R, Gaur SK, Nirmal K, Vij JC, Anand BS Repeated endoscopic sclerotherapy during active variceal bleeding. *Ann Surg* 1985; **202**, 708–11
6. Paquet KH, Feussner H. Endoscopic sclerosis and oesophageal balloon tamponade in acute haemorrhage from oesophageal-gastric varices, a prospective controlled randomized trial. *Hepatology* 1985, **5**: 580–3.
7. Sarin SK, Sachdev G, Nanda R Follow-up of patients after variceal eradication—a comparison of patients with cirrhosis, non-cirrhotic portal fibrosis and extrahepatic obstruction. *Ann Surg* 1986; **204**. 78–82.
8. Paquet KH. Open discussion on technical aspects of injection sclerotherapy. In: Westaby D, MacDougall BRD, Williams R, eds. *Variceal Bleeding*. London: Pitman Press: 1982; 215–17.
9. Conn HO. Ammonia tolerance in the diagnosis of oesophageal varices. A comparison of the endoscopic, radiologic and biochemical techniques *J Lab Clin Med* 1967, **70**: 442–51.
10. Sarin SK, Sachdev G, Nanda R, Batra SK, Anand BS A comparison of the two time schedules for endoscopic sclerotherapy, a prospective, randomized controlled clinical trial *Gut* 1986; **27**: 710–13.
11. Sarin SK, Nanda R, Sachdev G, Chari S, Anand BS, Broor SL Intravariceal versus paravariceal sclerotherapy. a prospective, controlled, randomised trial. *Gut* 1987, **28**: 657–62.
12. Snady H. The role of sclerotherapy in the treatment of oesophageal varices: personal experience and a review of randomized trials *Am J Gastroenterol* 1987; **82**: 813–22
13. Marshak RH, Linder AE, Marlansky D, eds. *Radiology of the Stomach*. Philadelphia. W. B. Saunders, 1983.
14. Baer JW, Smorrzaniuk E. Gastric varices appearing as intraluminal masses on computed trans-axial tomography. *Gastrointest Radiol* 1985; **10**. 345–6
15. Pagani JJ, Thomas JL, Bernardino ME CT manifestation of abdominal and pelvic venous collaterals *Radiology* 1982; **142**: 415–19.
16. MacDougall BRD, Theodossi A, Westaby D, Dawson JL, Williams R Increased long-term survival in variceal haemorrhage using injection sclerotherapy. *Lancet* 1982, **i**: 124–7.
17. Terblanche J, Northover JMA, Bornman P *et al.* A prospective controlled trial of sclerotherapy in the long-term management of patients after oesophageal variceal bleeding. *Surg Gynecol Obstet* 1979; **148**: 323–33.
18. Grobe JL, Kozarek RA, Sanowski RA, Le Grand J, Kovac A. Venography during endoscopic injection sclerotherapy of oesophageal varices. *Gastrointest Endosc* 1984; **30**. 6–8.
19. Kitano S, Terblanche J, Kahn D, Bornman PC. Venous anatomy of the lower oesophagus in portal hypertension: practical implications *Br J Surg* 1986, **73**: 525–31.
20. Johnson A, Simm JM, Stoddard CJ Is there a role for injection sclerotherapy in the presence of active bleeding? In: Westaby D, MacDougall BRD, Williams R, eds *Variceal Bleeding*. London: Pitman Press, 1982: 159–64.
21. Stray N, Jacobsen CD, Roselland A Injection sclerotherapy of bleeding oesophageal and gastric varices using a flexible endoscope. *Acta Med Scand* 1982; **211**: 125–9.
22. Yassin MY, Eita MS, Hussein AMT Endoscopic sclerotherapy for bleeding gastric varices *Gut* 1985; **26**: A 1105.
23. Sarin SK, Nanda R, Vij JC, Anand BS. Oesophageal ulceration after endoscopic sclerotherapy, a complication or an accompaniment? *Endoscopy* 1986, **18**: 44–5
24. Rorak G. Treatment of postsclerotherapy oesophageal ulcers with sucralfate. *Gastrointest Endosc* 1984; **30**: 9–10
25. Singal AK, Sarin SA, Misra SP, Broor SL. Ulceration after oesophageal and gastric variceal sclerotherapy—influence of sucralfate and other factors on healing. *Endoscopy* 1988, **20**. (in press)

Paper accepted 22 March 1988

Br. J. Surg. 1988, Vol. 75, August,
751–753

Trial of sclerosing agents in patients with oesophageal varices

Forty-five cirrhotic patients with oesophageal varices underwent endoscopic injection sclerotherapy in a prospective randomized trial carried out to compare two sclerosing agents (5 per cent ethanolamine oleate and 2 per cent sodium tetradecyl sulphate (STD)) with respect to safety, efficacy and complications. Twenty-three patients were allocated to the ethanolamine group and twenty-two to the STD group. The rate of control of acute bleeding was 100 per cent (6/6) in the ethanolamine group and 75 per cent (3/4) in the STD group. There was a significantly lower rate of postinjection bleeding after the over-tube was removed at the initial session of sclerotherapy when ethanolamine was injected 0/23 versus *7/22, 32 per cent;* $P<0\cdot01$*) and at the second session there was a significantly* ($P<0\cdot01$) *higher rate of jet-like bleeding from injection sites in the STD group (6/21, 29 per cent) than in the ethanolamine group (0/22). The disappearance rate of red colour signs 1 week after the initial session of sclerotherapy in the ethanolamine group was 100 per cent and 62 per cent in the STD group. Early oesophageal ulcers developed less frequently in the ethanolamine group (0 and 9 per cent) than in the STD group (24 per cent and 43 per cent both after the initial* ($P<0\cdot05$) *and the second session of sclerotherapy* ($P<0\cdot01$)*). Early bleeding from an oesophageal ulcer occurred only in the STD group (5/21, 24 per cent) before the third session of sclerotherapy* ($P<0\cdot05$). *The rate of early mortality did not differ between the two groups. We conclude that ethanolamine seems to be safer and more efficacious than STD for sclerosing oesophageal varices.*

Keywords: Sclerotherapy, 5 per cent ethanolamine oleate, 2 per cent sodium tetradecyl sulphate

**S. Kitano, Y. Iso,
H. Yamaga,
M. Hashizume,
H. Higashi and
K. Sugimachi**

*Department of Surgery II, Kyushu
University Faculty of Medicine,
Fukuoka 812, Japan
Correspondence to:*
Dr S. Kitano

Various methods and techniques for sclerosing oesophageal varices have been reported[1–5]. The over-tube technique[3,4] seems to provide a rapid and safe method of endoscopic injection sclerotherapy, even in patients with massive bleeding. To halt the acute variceal bleeding, various sclerosants[1,2,6,7] have been used for intra- or paravariceal injections. In the United States, sodium tetradecyl sulphate (STD) is widely used, the objective being to induce thrombosis of the variceal channels. Ethanolamine oleate is at present the most commonly used sclerosant in South Africa, Great Britain and Japan.

The present prospective randomized trial was undertaken to compare the efficacy and related complications of the two sclerosing solutions, 5 per cent ethanolamine oleate and 2 per cent STD, in repeated injection sclerotherapy.

Patients and methods

From October 1986 to February 1987, 45 cirrhotic Japanese with portal hypertension and oesophageal varices were treated in our clinics. On entering the trial, the consent of each patient was obtained and classification was made according to a modification of Child's grading system[8]. Twenty-three patients were randomly allocated to the ethanolamine group, using a system of randomized numbers, and twenty-two to the STD group.

Patients with 'risky' varices were given prophylactic injections, according to our published criteria[9]. At approximately 1-week intervals, sclerotherapy was repeated as described elsewhere[4], until oesophageal varices were eradicated. The initial session of sclerotherapy was carried out using a newly designed transparent over-tube[10] (a K-S tube, Olympus, Japan) which facilitates precise injection of sclerosant into the oesophageal varices, under a clear field of vision. Subsequent injections were performed with the free-hand technique, using the GIF Q10 series panendoscope (Olympus, Japan). The sclerosant, 5 per cent ethanolamine (prepared in Kyushu University Hospital) or 2 per cent STD (prepared in the National Nagoya Hospital), was injected directly into the varices in the early stage of sclerotherapy and later into the superficial layer of the oesophageal submucosa, so that superficial ulceration would develop in the lower oesophagus, this being the endpoint of sclerotherapy (see Discussion). Diazepam (5–10 mg) and pentazocine (30 mg) were given intravenously after topical anaesthesia with 4 per cent Xylocaine (Astra, UK), at all sclerotherapy sessions. The same technique was used to inject sclerosant throughout the course of repeated sclerotherapy.

Volume of sclerosant injected, number of sessions required for eradication of the varices, and frequency of bleeding during the course of sclerotherapy were recorded. With respect to the assessment of complications and efficacy, particular attention was directed to postinjection bleeding, retrosternal pain requiring opiate analgesics, pyrexia (>38°C), pleural effusion, oesophageal ulcer and stricture formation. From two to four sessions of endoscopy were carried out at 1-week intervals to confirm eradication of the varices. Statistical analysis was made using the χ^2 test and Student's t test.

Results

Characteristics of the two groups

The clinical characteristics of the two groups are shown in *Table 1*. The two groups were comparable with regard to age, sex and severity of liver disease. Six patients in the ethanolamine group and four in the STD group were treated with sclerotherapy on an emergency basis, and three and seven patients respectively were treated under elective conditions. Prophylactic injections were given to 14 patients in the ethanolamine group and 11 in the STD group, as the endoscopic findings showed a significant risk of bleeding. There were 12 patients with a hepatoma (5 in the ethanolamine, 7 in the STD group) and the lesion was not resectable for functional and/or anatomical reasons (poor liver function, huge or multiple hepatomas).

0007–1323/88/080751–03$3.00 © 1988 Butterworth & Co (Publishers) Ltd

Table 1 *Clinical characteristics of the two groups*

	Ethanolamine	Sodium tetradecyl sulphate
Number of patients	23	22
Age (mean, years)	57·6	55·3
Sex (M/F)	18/5	17/5
Liver disease		
Cirrhosis	23	21
Chronic active hepatitis	0	1
Liver function (mean ± s.d.)		
Albumin (g/dl)	3·2±0·6	3·3±0·4
Bilirubin (mg/dl)	1·5±1·3	1·6±1·4
ICG R15 (%)	36·1±12·2	33·0±16·3
Child's score	8·1±1·8	7·9±1·8
Child's classification		
A	5	4
B	11	13
C	7	5
Size of varices (Reference 9)		
Huge (F3)	10	8
Moderate (F2)	13	14

ICG: Indocyanine green test (normal 0–10%)

Table 2 *Endoscopic findings 1 week after the initial session of repeated sclerotherapy*

Findings	Ethanolamine	Sodium tetradecyl sulphate	*P*
Red colour signs (+)	0/23	8/21 (38)	<0·01
Early ulcer	0/23	5/21 (24)	<0·05

Percentages in parentheses

Control of acute variceal bleeding and postinjection bleeding

Acute bleeding was readily controlled with an accurate injection of 5 per cent ethanolamine via a K-S tube in all 6 patients and in 3 of 4 patients injected with 2 per cent STD: the difference was not statistically significant. The one patient who had continuous bleeding from a ruptured site on the oesophageal varix died 12 h later; the STD had been injected intravariceally.

When the over-tube was removed after compressing the injection sites for 3 min, seven patients (32 per cent) in the STD group had continued bleeding and additional injections of 2–3 ml of STD were given to arrest bleeding from the injection sites. There were no such cases in the ethanolamine group. Here the difference was significant ($P<0{\cdot}01$).

Endoscopic findings after the initial session of sclerotherapy

Table 2 shows the endoscopic findings 1 week after injection. The oesophageal mucosa covering the varices where the sclerosants had been injected was thick and swollen (presumably the result of thrombosis and inflammation which resulted in the disappearance of red colour signs on the varices) in all the 23 patients in the ethanolamine group. In the STD group, the oesophageal varices were shown endoscopically to be patent with little inflammation and showed a considerable degree of red coloration in 8 of the 21 patients. In the ethanolamine group, there was a significantly higher rate ($P<0{\cdot}01$) of disappearance of red coloration, compared with the rate in the STD group (100 per cent *versus* 62 per cent).

In accordance with the endoscopic findings, jet-like bleeding from the injection sites at the second session of sclerotherapy was evident more frequently in the STD group (6/21, 29 per cent) than in the ethanolamine group (0/22; $P<0{\cdot}01$), excluding one patient in each group who died before the second session of sclerotherapy. Oesophageal ulcers were observed in 5 of 21 patients in the STD group, but none in the ethanolamine group, 1 week after the initial session of sclerotherapy. The difference was statistically significant ($P<0{\cdot}05$).

Mortality rates

Three of the 45 patients died during the course of sclerotherapy. In the ethanolamine group, one patient died of liver failure 10 days after the initial sclerotherapy to control acute variceal bleeding. In the STD group, there were two early deaths: one due to uncontrollable variceal bleeding and another due to liver failure after two sessions of sclerotherapy. One each in the ethanolamine and STD group died of liver failure and hepatoma 4 months and 2 months respectively after the initial session of sclerotherapy. At the time of writing, 21 and 19 patients in the ethanolamine and STD groups, respectively, are alive without any episode of bleeding.

Number of sclerotherapy sessions, period and volume of the sclerosants

The number of sclerotherapy sessions, period and volume of the sclerosants used during the course of sclerotherapy did not differ between the two groups (*Table 3*). At the late stage of sclerotherapy, any residual mucosa was obliterated with spread of the ethanolamine, whereas with STD the mucosa remained, despite the administration of a sufficient volume. The rate of attainment of superficial ulcer formation (our proposed endpoint) in the lower oesophagus was higher ($P<0{\cdot}01$) in the ethanolamine group (100 per cent) than in the STD group (60 per cent).

Complications in the two groups (Table 4)

Early oesophageal ulcer developed less frequently in the ethanolamine group than in the STD group after both the initial session ($P<0{\cdot}05$) and the second session of sclerotherapy ($P<0{\cdot}01$). Early bleeding from an oesophageal ulcer occurred only in the STD group (5/21, 24 per cent) before the third session of sclerotherapy: here the difference was statistically significant ($P<0{\cdot}05$). One patient in whom the variceal bleeding had been

Table 3 *Number of sclerotherapy sessions, period, volume of the sclerosants (mean ± s.d.) and development of superficial ulcer in the lower oesophagus*

	Ethanolamine	Sodium tetradecyl sulphate
Total number of sessions	100	91
No. of sclerotherapy sessions	4·5±1·1	4·4±1·1
(range)	(3–7)	(3–6)
No. of weeks	4·9±1·2	5·0±1·4
(range)	(3–7)	(3–8)
Total volume (ml)	66·8±15·2	60·9±19·2
(range)	(45–105)	(35–115)
Mean volume (ml)		
Initial session	24·3±3·9	23·6±2·8
Second session	17·7±5·1	16·1±2·9
Third session	12·0±3·2	11·0±5·3
Fourth session	10·4±3·8	7·8±4·6
Superficial ulceration	22/22 (100%)	12/20 (60%)

* $P<0{\cdot}01$

Table 4 *Complications of sclerotherapy*

	Ethanolamine	Sodium tetradecyl sulphate	*P*
Early bleeding	0/22	5/21 (24)	<0·05
Early ulcer (after two sessions)	2/22 (9)	9/21 (43)	<0·01
Pain	11/100 (11)	9/91 (10)	n.s.
Pyrexia (>38°C)	10/100 (10)	8/91 (9)	n.s.
Stricture	3/22 (14)	2/21 (10)	n.s.
Pleural effusion	11/22 (50)	9/21 (43)	n.s.

One patient in each group died and related data were not used
Percentages in parentheses; n.s., not significant

halted with sclerotherapy had a rebleeding episode from an oesophageal ulcer 6 days after the index bleed. Two Child's C patients and one Child's B patient had bleeding episodes 1, 2 and 5 days after the second session of sclerotherapy. Another patient in Child's C grade to whom prophylactic sclerotherapy had been given had a bleeding episode from an oesophageal ulcer at the time of the third session of sclerotherapy. These bleeding episodes were all controlled with an additional session of sclerotherapy, using STD. There were no major complications related to sclerotherapy (except for the above-mentioned oesophageal ulcers) in either group. Stricture was observed endoscopically in three and two patients of the ethanolamine and STD group, respectively. Dilatation was readily accomplished with two or three sessions of bougienage. No patient required thoracic drainage for the asymptomatic pleural effusion which was sometimes evident on the chest radiograph.

Discussion

In this prospective randomized study, half the patients were given prophylactic injections because of 'risky' varices. In particular, red coloration was taken as an indication for prophylactic treatment[2,11].

There are two major techniques of sclerotherapy for oesophageal varices—intravariceal injection to thrombose the varices[1] and eventually to prevent further bleeding, and submucosal injection[2] adjacent to the varices, resulting in submucosal oedema which is expected to halt acute bleeding while subsequent fibrous thickening of the mucosa prevents late bleeding. With intravariceal injection, precise injection of the sclerosant into varices is essential for success.

Fearon and Sass-Kortsak[12] compared three different sclerosants, including 5 per cent ethanolamine and STD, and found that the latter was superior with regard to efficacy and complications. In a prospective randomized trial[13] we found that ethanolamine was superior to polidocanol as a sclerosant when injected intravariceally to control acute bleeding and to prevent recurrent bleeding.

Jensen[14], compared the sclerosing agents 5 per cent ethanolamine, 5 per cent sodium morrhuate, 1·5 per cent STD and 50 per cent dextrose, in a canine model with portal hypertension, and found that STD and ethanolamine were the most efficacious agents, although the former was associated with a 40 per cent incidence of ulceration. This high rate of ulceration after injection of STD was comparable with the rate of occurrence in our patients, in whom early oesophageal ulceration occurred in 24 per cent of the STD group at an early stage in repeated sclerotherapy. We injected a sufficient volume of STD into all variceal channels in the lower oesophagus to completely thrombose the varices. The rate of occurrence of oesophageal bleeding during the course of repeated sclerotherapy was also comparable with data in other reports[6,7].

Our previous data[15] suggested that destruction of the mucosa might be the endpoint of sclerotherapy when trying to prevent recurrence of varices. With this technique, the sclerosant is expected to thrombose the varices at an early stage and to obliterate the oesophageal mucosa at a later stage of repeated sclerotherapy. This would destroy the oesophageal mucosa at areas where varices can recur in the long term. In the present series, the oesophageal mucosa was obliterated by repeated sclerotherapy in all patients in the ethanolamine group, but in only 60 per cent in the STD group. Hence, there may be a recurrence of oesophageal varices[3] after STD injection as minute venous channels remain in the residual mucosa[16].

At the late stage of repeated sclerotherapy, endoscopy showed that ethanolamine had spread in the submucosal tissue of the oesophagus after injection into any mucosa which remained visible after the thrombosed oesophageal varices had become necrotic. The STD remained limited to the area injected. Differences in the properties of the sclerosants may explain why superficial circumferential ulceration of the lower oesophagus developed less frequently in the STD group than in the ethanolamine group at the late stage of repeated sclerotherapy.

In conclusion, we found ethanolamine to be superior to STD as a sclerosant when injected intravariceally using the transparent over-tube technique.

Acknowledgements

We thank Dr K Ohtsubo, Kyushu University, Dr M. Ohashi, National Nagoya Hospital, for preparing the sclerosants and M. Ohara for critical reading of the manuscript.

References

1. Terblanche J, Northover JMA, Bornman PC *et al* A prospective evaluation of injection sclerotherapy in the treatment of acute bleeding from esophageal varices. *Surgery* 1979; **85** 239–45
2. Paquet KJ. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices—a prospective controlled randomized trial. *Endoscopy* 1982; **14**: 4–5
3. Westaby D, Macdougall BRD, Williams R. Improved survival following injection sclerotherapy for esophageal varices Final analysis of a controlled trial. *Hepatology* 1985; 5. 827–30.
4. Kitano S, Koyanagi N, Iso Y *et al.* Prospective randomized trial comparing two injection techniques for sclerosing oesophageal varices: over-tube and free-hand. *Br J Surg* 1987, **74**: 603–6.
5. Crafoord C, Frenckner P New surgical treatment of varicose veins of the oesophagus *Acta Otolaryngol* 1939; **27** 422–9.
6. Korula J, Balart LA, Radvan G, Zweiban BE, Larson AW, Kao HW. A prospective, randomized controlled trial of chronic esophageal variceal sclerotherapy. *Hepatology* 1985; **5**: 584–9
7. Sivak MV, Stout DJ, Skipper G. Endoscopic injection sclerotherapy (EIS) of esophageal varices: *Gastrointest Endosc* 1981; **27**: 52–7.
8. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni HC, Williams R Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973, **60**. 646–9
9. Beppu K, Inokuchi K, Koyanagi N *et al.* Prediction of variceal hemorrhage by esophageal endoscopy *Gastrointest Endosc* 1981, **27**: 213–8.
10. Kitano S, Sugimachi K. A rapid and relatively safer method of sclerosing esophageal varices utilizing a new transparent tube *Am J Surg* 1987; **153**: 317–20.
11. Inokuchi K. Prophylactic portal non-decompression surgery in patients with esophageal varices—an interim report. *Ann Surg* 1984, **200**: 61–5.
12. Fearon B, Sass-Kortsak A. The management of esophageal varices in children by injection of sclerosing agents *Ann Otol Rhinol Laryngol* 1959; **68**: 909–15.
13. Kitano S, Iso Y, Koyanagi N, Higashi H, Sugimachi K Ethanolamine oleate is superior to polidocanol (aethoxysklerol) for endoscopic injection sclerotherapy of esophageal varices: A prospective randomized trial. *Hepato-Gastroenterol* 1987; **34**: 19–23
14. Jensen DM. Sclerosants for injection sclerosis of esophageal varices *Gastrointest Endosc* 1983, **29** 315–17
15. Kitano S, Koyanagi N, Iso Y, Higashi H, Sugimachi K Prevention of recurrence of esophageal varices after endoscopic injection sclerotherapy with ethanolamine oleate *Hepatology* 1987, **7**. 810–5.
16. Kitano S, Terblanche J, Kahn D, Bornman P. Venous anatomy of the lower oesophagus in portal hypertension practical implications *Br J Surg* 1986; 73: 525–31.

Paper accepted 17 February 1988

Br. J. Surg. 1988, Vol. 75, August, 754–757

Intramural haematoma of the alimentary tract in children

S. Chittmittrapap, B. Chandrakamol and S. Chomdej*

*Division of Paediatric Surgery, Department of Surgery and *Department of Radiology, Chulalongkorn University Hospital, Bangkok, Thailand*

Correspondence to:
Dr S. Chittmittrapap, Department of Surgery, Chulalongkorn University Hospital, Bangkok 10500, Thailand

Thirteen children with intramural haematoma of the alimentary tract were treated in Chulalongkorn University Hospital during an 8-year period (1978–1986). A history of trauma was obtained in 11 cases, 1 case presented as a result of a coagulation defect secondary to a haematotoxic snake bite and no causative factor was apparent in 1 patient. Profound vomiting with abdominal pain is the typical presentation. Upper gastrointestinal contrast study is usually characteristic and diagnostic. Conservative treatment was successful in 12 of the cases with no morbidity and mortality.

Keywords: Intramural haematoma, duodenal haematoma, duodenal injury, duodenal obstruction

Intramural haematoma of the alimentary tract has only been sporadically reported in the literature. A localized collection of blood which extravasates into subserosa, submucosa and interstitial tissues of the intestine is most commonly found in children after blunt trauma and is the cause of a variable degree of duodenal obstruction. Profound vomiting, which is a late clinical manifestation, supports a correct diagnosis confirmed by barium meal. The acute presentation of abdominal pain after recent abdominal blunt trauma is more difficult to diagnose. Associated serious injury to intra-abdominal organs requiring surgical intervention must be excluded. A conservative approach to the management of intramural haematoma has been suggested in many recent reports.

This is a review of our experience in managing intramural haematoma of the alimentary tract during the last 8 years.

Patients and methods

The records of children, admitted to Chulalongkorn University Hospital between January 1978 and December 1986, with intramural haematoma of the alimentary tract were retrospectively reviewed. The clinical presentation, aetiology, clinical course and outcome of these patients are reported

Results

Thirteen children, seven boys and six girls had intramural haematoma of the alimentary tract diagnosed; their ages ranged from 2 to 14 years (mean 7·8 years). A history of trauma was obtained in 11 cases (85 per cent). In three cases, the nature of the injury was only realized after the diagnosis had been made. Seven patients fell against hard objects at play; two boys were physically abused. Intramural duodenal haematoma was a result of a coagulation defect due to a greenpit viper (haematotoxic) snake bite in one case. No specific cause was identified in the other patient (*Table 1*).

Four children presented with abdominal pain and vomiting immediately or recently after trauma and physical examination revealed marked tenderness over the epigastric area without signs of peritonitis. Nasogastric aspiration revealed blood-stained gastric contents in one. Upper gastrointestinal contrast study, performed about 18–48 h after admission when the patient's condition was stable, was diagnostic in all and excluded bowel perforation. Ultrasonography was also used in five patients to exclude serious associated injuries particularly of the pancreas.

The other eight cases presented with severe vomiting three or more days after injury. Four were dehydrated on admission. Mild epigastric tenderness alone was detected. Plain abdominal X-ray and barium meal supported the clinical diagnosis of intramural haematoma.

One case (patient number 1) presented with vomiting and abdominal pain without definite history of trauma. Conservative treatment was initiated, but his abdominal pain became worse and laparotomy was required for diagnosis.

Laboratory data (*Table 2*) show that the haematocrit and white blood cell count were normal at the time of admission in all cases. The serum amylase was elevated in four cases with associated pancreatic injuries shown by ultrasonography.

Plain abdominal radiograph was unremarkable in the children who presented at an early stage but suggested duodenal obstruction in the delayed presentation group. A gastrointestinal contrast study, performed in the last 12 cases, was characteristic and diagnostic of intramural haematoma. Associated injuries are presented in *Table 3*.

Twelve patients (92 per cent) were successfully treated without operation, even those with associated pancreatic injuries. All the patients recovered and the pancreatic injuries resolved spontaneously. Only one case which is the first case of this report had undergone laparotomy for suspected peritonitis. Evacuation of a duodenal haematoma was performed and postoperative recovery was uneventful.

Discussion

Intramural haematoma of the alimentary tract of differing aetiology occurs mainly in children. Blunt abdominal non-accidental injury is the most common cause in all reports to date[1–4]. The more frequent but less severe trauma, the weakness of abdominal wall musculature and the splayed costal margin in children may account for this. Intramural haematoma as a result of child abuse is now increasing[5,6]. It may present spontaneously in haemophiliac patients, patients with coagulation defect from anticoagulant therapy, blood dyscrasias, aplastic anaemia and haematotoxic snake bite[2,7,8]. This condition has also been reported after endoscopic intestinal biopsy[9]. Shearing force causes bleeding from small vessels which extravasate into muscularis, subserosal or submucosal layers[10,11]. A small haematoma may absorb fluid as the haemoglobin breaks down or may increase in size to be sufficiently large to obliterate the lumen, hence the delayed presentation of intestinal obstruction[2]. The common bile duct may even become obstructed[12].

Laboratory tests are introduced but they are usually unhelpful. In most reports, the amount of blood loss is small with no significant change in haemoglobin level and the white blood cell count is not elevated. A few cases of intramural

---

Presented at the 6th Biennial Congress of the Association of Surgeons of Southeast Asia, Bangkok, February 1987.

0007-1323/88/080754-04$3 00

Table 1 *Clinical data of patients with intramural haematoma of the duodenum*

Case no.	Sex	Age (years)	Aetiology (type of injury)	Symptoms	Interval between trauma and symptoms	Interval between trauma and admission	Non-surgical clinical diagnosis	Clinical diagnosis by surgeon
1	M	9	Unknown	Vomiting, abdominal pain	?	4 days (?)	Haemorrhagic fever	Peritonitis caused
2	M	7	Pedestrian, hit by a car	Abdominal pain, vomiting	1 day	2 days	Blunt abdominal trauma	Abdominal trauma
3	F	8	Fell against bicycle handle bar	Vomiting	1 day	4 days	Gut obstruction	Gut obstruction
4	M	6	Battered by baby-sitter	Haematemesis, abdominal pain	9 h	12 h	Abdominal trauma IHD suspected	IHD
5	M	6	Battered by stepfather	Vomiting	?	3 days (?)	Vomiting caused?	Gut obstruction
6	F	13	Fell on gymnastic bar*	Vomiting	2 days	7 days	Typhoid fever	IHD
7	F	2	Fell against floor*	Vomiting	2 days	5 days	High gut obstruction	IHD
8	M	5	Fell from house (4 m high)	Vomiting, abdominal pain	6 h	18 h	Pancreatic injury	Pancreatic injury
9	F	12	Fell against bicycle handle bar	Vomiting	2 days	4 days	Acute gastro-enteritis	IHD
10	M	14	Coagulation defect caused by greenpit viper bite	Vomiting	?	?	IHD	IHD
11	M	6	Fell against bicycle handle bar	Vomiting	1 day	3 days	Acute gastro-enteritis	IHD
12	F	9	Fell from seesaw	Abdominal pain, vomiting	1 day	2 days	IHD with pancreatic injury	IHD with pancreatic injury
13	F	4	Fell against chair	Abdominal pain, vomiting	1 day	3 days	Abdominal pain	IHD

* History of trauma was obtained from retrospective interview; IHD, intramural haematoma of the duodenum

Table 2 *Laboratory data and investigations*

Case no.	Haematocrit (%)	White cell count	Serum amylase* (units/l)	Other data*	Plain abdominal X-ray	Upper gastrointestinal study
1	44	8 400 (N77, band 6)	—	—	Unremarkable	—
2	40	10 000 (N82, L18)	—	—	Paralytic ileus	IHD, partial obstruction
3	38	15 300 (N94, L6)	112·3 (88–245)	Lipase 2·15 (0·5–1·5)	Partial high gut obstruction	IHD, partial obstruction
4	33	14 150 (N92, L8)	300 (45–200)	—	Duodenal obstruction, no air in distal bowel	IHD, complete obstruction
5	36	9 800 (N80, L20)	1123 (45–200)	US: swelling pancreas	Unremarkable	IHD, oedema duodenum
6	38	6 200 (N60, L40)	136 (45–200)	—	Partial high gut obstruction	IHD, thumb print defect
7	36	3 350 (N60, L40)	200 (140–390)	—	Ileus of upper abdomen	IHD, partial obstruction
8	35	14 750 (N83, L17)	1633 (140–390)	US: pancreatic pseudocyst	Dilated stomach, duodenum, soft tissue density LUQ	IHD, partial obstruction
9	40	11 200 (N85, L15)	174 (140–390)	—	Duodenal obstruction	IHD, nearly complete obstruction
10	32	6 600 (N79, L21)	—	Prolonged prothrombin bleeding time	Duodenal obstruction	IHD, nearly complete obstruction
11	39	17 300 (N84, L16)	1032 (140–390)	Lipase 5·81 (0·5–1·5) US: haematoma, pancreatic head	Dilated stomach, no air in distal bowel	IHD, complete obstruction
12	38	21 100 (N91, L9)	2650 (140–390)	Urine amylase 35 157, US: swelling pancreas	Partial high gut obstruction	IHD
13	39	18 300 (N84, L16)	105 (140–390)		Dilated stomach, no air in distal bowel	IHD, complete obstruction

* Normal values in parentheses; IHD, intramural haematoma of the duodenum; US, ultrasonography; LUQ, left upper quadrant

haematoma have a mildly elevated serum amylase level. High serum amylase indicates associated pancreatic injury[6,10,13].

Upper gastrointestinal contrast study is mandatory, usually characteristic and diagnostic. It may show complete obstruction with tapering indicating an intramural mass (*Figure 1*). Felson and Levin[14] described the striking characteristic 'coil-spring' pattern (*Figure 2*) due to collection of blood in the mucosal folds. Wiot *et al.*[8] termed the appearance of thickening of mucosal folds due to intramural haematoma collection as a picket fence or stacked coins (*Figure 3*). The stomach may be displaced forward and upward if there is pancreatic haematoma or pseudocyst. Contrast study is useful to exclude bowel

Table 3 *Clinical course and management*

Case no.	Definitive diagnosis by:	Location of haematoma	Associated injuries	Treatment	NPO period (days)	Results
1	Laparotomy	2nd, 3rd parts of duodenum	Haematoma in transverse colon, mesocolon, mesentery	Laparotomy, evacuation of blood	4	Recovery
2	UGI study	3rd part of duodenum	—	Conservative	4	Recovery
3	UGI study	3rd part of duodenum	—	Conservative	4	Recovery
4	UGI study	2nd, 3rd parts of duodenum	—	Conservative	9	Discharge 15 days after admission—re-admitted for vomiting 1 day later. UGI: no obstruction but delayed barium passage
5	UGI study	2nd, 3rd parts of duodenum	Pancreas (pseudocyst)	Conservative	5	Recovery, US follow-up: resolution of cyst
6	UGI study	3rd part of duodenum, jejunum	—	Conservative	3	Recovery
7	UGI study	3rd, 4th parts of duodenum, proximal jejunum	—	Conservative	8	Recovery
8	UGI study	2nd, 3rd parts of duodenum	Pancreas (pancreatitis, pseudocyst)	Conservative	7	Recovery, US follow-up: resolution of cyst
9	UGI study	2nd part of duodenum	—	Conservative	6	Recovery
10	UGI study	2nd part of duodenum	—	Conservative	7	Recovery
11	UGI study	1st, 2nd parts of duodenum	Pancreas (haematoma 2 × 4 cm at pancreatic head)	Conservative	12	Recovery: haematoma resolution
12	UGI study	2nd, 3rd parts of duodenum	Pancreas (traumatic pancreatitis)	Conservative	8	Recovery
13	UGI study	2nd, 3rd parts of duodenum	—	Conservative	5	Recovery

UGI, upper gastrointestinal; NPO, nil per mouth; US, ultrasonography

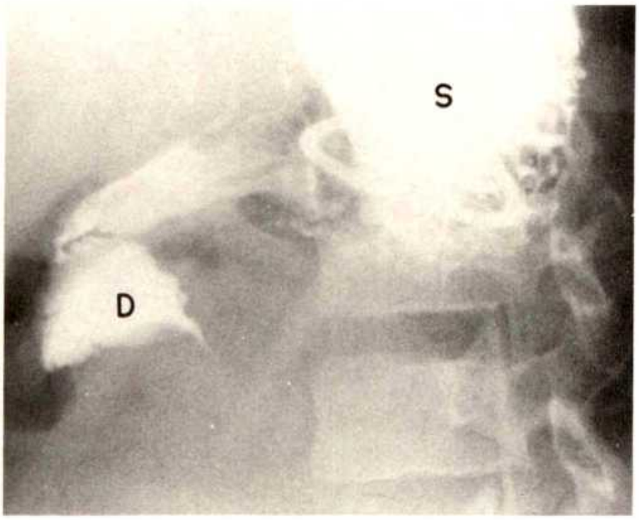


Figure 1 *Contrast study showing tapering of the second part of the duodenum with nearly complete obstruction caused by the intramural mass. S, stomach; D, duodenum*

perforation. Larger haematomata may be detected by ultrasonography which also may identify associated pancreatic injury.

Some authors have suggested that surgery is necessary to exclude duodenal perforation which carries a high morbidity and mortality. Early intervention may also shorten hospital stay[1,15,16]. Evacuation of blood clot with or without gastroenterostomy has also been advocated. Altner[17] and Mathewson[18] stated that haematoma may produce a cicatrizing inflammatory reaction capable of permanently deforming the intestine or scarring the intestinal wall. Many recent reports[3,5,6,19–22] suggest that conservative management is appropriate in most cases and no complications are encountered. Our experience in managing these cases supports this opinion.

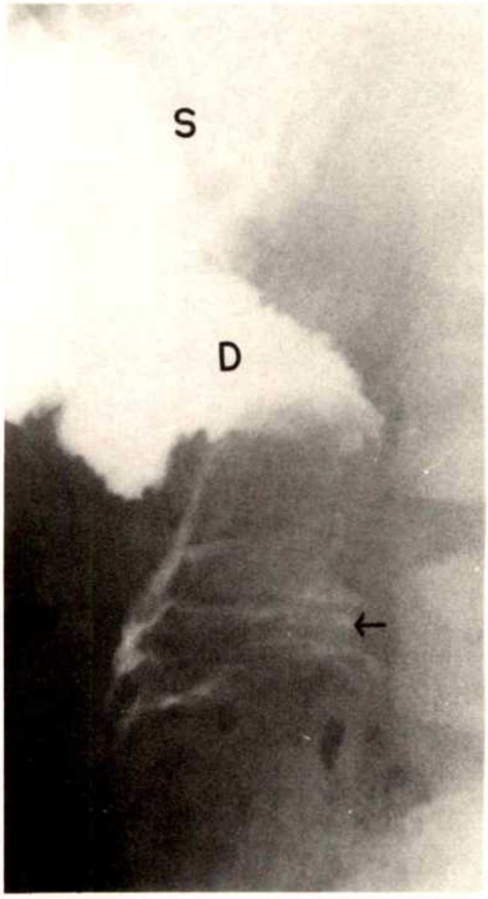


Figure 2 *Contrast study showing the characteristic 'coil spring' sign (arrow). S, stomach; D, duodenum*

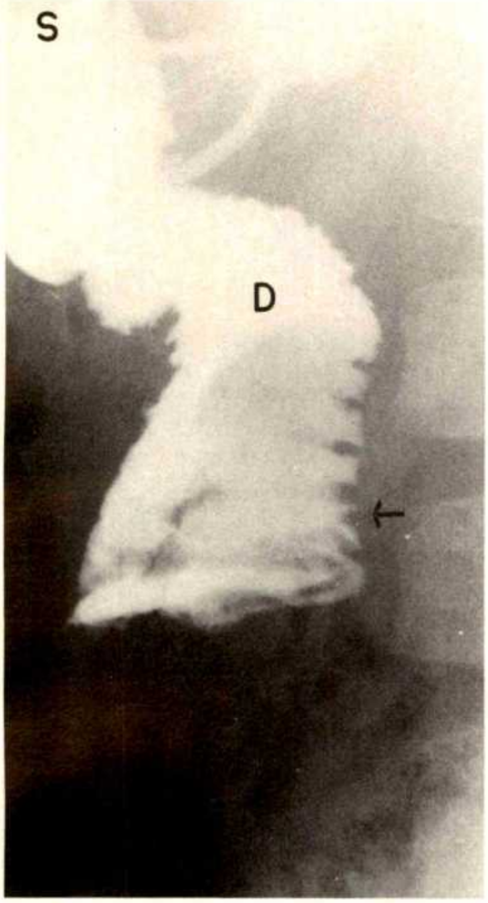


Figure 3 *The contrast medium outlined the thickened duodenal mucosa due to intramural blood collection, the 'picket fence' appearance (arrow). S, stomach; D, duodenum*

Laparotomy is recommended only in patients in whom there is a high suspicion of intestinal perforation. Altner[17] suggested that surgery should be undertaken, if conservative treatment is not effective, within a reasonable length of time before a complete organization of haematoma occurs. Nevertheless most reports confirm that conservative treatment is satisfactory despite prolonged decompression.

Acknowledgement

The authors wish to thank Mr R. Springall, Institute of Child Health, University of London, for his kindly assistance in the preparation of the manuscript.

References

1. Freeark RJ, Corley RD, Norcross WJ, Strohl L. Intramural hematoma of the duodenum. *Arch Surg* 1966; **92**: 463–75.
2. Judd OR, Taybi H, King H. Intramural hematoma of the small bowel. *Arch Surg* 1964; **89**: 527–35.
3. Janson KL, Stockinger F. Duodenal hematoma. Critical analysis of recent treatment technics. *Am J Surg* 1975; **129**: 304–8.
4. Webb AJ, Taylor JJ. Traumatic intramural haematoma of the duodenum. *Br J Surg* 1967; **54**: 50–6.
5. Mahour GH, Woolley MM, Gans SL, Payne VC. Duodenal hematoma in infancy and childhood. *J Pediatr Surg* 1971; **6**: 153–60.
6. Woolley MM, Mahour GH, Timothy S. Duodenal hematoma in infancy and childhood. Changing etiology and changing treatment. *Am J Surg* 1978; **136**: 8–14.
7. Beamish RE, McCreath ND. Intestinal obstruction complicating anticoagulant therapy. *Lancet* 1961; **ii**: 390–2.
8. Wiot JF, Weinstein AS, Felson B. Duodenal hematoma induced by coumarin. *Am J Roentgenol* 1961; **86**: 823–31.
9. Ben-Baruch D, Powsner E, Cohen M, Dintsman M. Intramural hematoma of duodenum following endoscopic intestinal biopsy. *J Pediatr Surg* 1987; **22**: 1009–10.
10. Izant R, Drucker W. Duodenal obstruction due to intramural hematoma in children. *J Trauma* 1964; **4**: 797–813.
11. Williams R, Sargent BA. The mechanism of intestinal injury in trauma. *J Trauma* 1963; **3**: 288–94.
12. Parrish RA, Edmondson HT, Moretz WH. Duodenal and biliary obstruction secondary to intramural hematoma. *Am J Surg* 1964; **108**: 426–30.
13. Stewart DR, Byrd CL, Schuster SR. Intramural hematoma of the alimentary tract in children. *Surgery* 1970; **68**: 550–7.
14. Felson B, Levin EJ. Intramural hematoma of duodenum, a diagnostic roentgen sign. *Radiology* 1954; **63**: 823–31.
15. Devroede GJ, Tirol FT, Lorusso VA, Narducci AE. Intramural hematoma of duodenum and jejunum. *Am J Surg* 1966; **112**: 947–52.
16. Golding MR, de Jong P, Parker JW. Intramural hematoma of the duodenum. *Ann Surg* 1963; **157**: 573–8.
17. Altner PC. Constrictive lesions of the colon due to blunt trauma to the abdomen. *Surg Gynecol Obstet* 1964; **118**: 1257–8.
18. Mathewson C Jr. Discussion on Woolley MM, Mahour GH, Timothy S (reference 6).
19. Vellocott KD. Intramural haematoma of the duodenum. *Br J Surg* 1980; **67**: 36–8.
20. Holgerson LO, Bishop HC. Nonoperative treatment of duodenal hematomata. *J Pediatr Surg* 1977; **12**: 11–18.
21. Nielsen IM. Intramural hematoma of the duodenum treated conservatively. *Acta Chir Scand* 1980; **46**: 303–5.
22. Winthrop AL, Wesson DE, Filler RM. Traumatic duodenal hematoma in the pediatric patient. *J Pediatr Surg* 1986; **21**: 757–60.

Paper accepted 10 April 1988

Br. J. Surg. 1988, Vol. 75, August,
758–759

Perforated gastric ulcer

C. Lanng,
C. Palnæs Hansen*,
A. Christensen†,
C. S. Thagaard†,
M. Lassen‡, A. Klærke§,
H. Tønnesen¶ and
S. E. Ostgaard‖

*Department of Surgery I, Kommunehospitalet, *Department of Surgery C, Rigshospitalet and †Department of Surgery D, Glostrup Hospital, Copenhagen; ‡Department of Surgery A, Odense Sygehas, Odense C; §Department of Surgery A, Ålborg Hospital Afsnit Syd, Ålborg; ¶Department of Gastrointestinal Surgery, Hvidovre Hospital, Hvidovre; ‖Department of Surgery L, Århus Kommunehospital, Århus, Denmark*

Correspondence to: Dr C. Lanng,
Ryesgade 25 D, 4.tv.,
Copenhagen N, 2200 Denmark

A retrospective study is presented of 297 patients operated upon for perforated benign gastric ulcer in Denmark from 1975 to 1984. Male:female ratio was 0·9:1, mean age 64·2 years. The numbers of gastric and prepyloric perforations were almost equal (156:141), but gastric perforations were more frequent in elderly women and prepyloric perforations in younger men. Simple closure was performed in 83 per cent of the patients, gastric resection in 14 per cent and simple closure and vagotomy in 3 per cent. The postoperative mortality rate was 21 per cent and was related to the high proportion of elderly patients with concurrent diseases and delayed treatment.

Keywords: Perforated peptic ulcer, gastric ulcer, mortality, treatment

Twenty per cent of perforated peptic ulcers are confined to the stomach[1–4]. Gastric perforation still carries a high mortality despite improvement in surgical treatment and intensive care. The aim of the present study was to evaluate the outcome of patients admitted with gastric perforation of peptic ulcer disease with regard to age, complications and operative treatment.

Patients and methods

The report comprises 297 patients from seven departments of gastrointestinal surgery in Denmark operated on for perforated benign gastric ulcer during the 10-year period 1975 to 1984. The study included all patients with perforated ulcer proximal to the pyloric ring. Perforations were classified as prepyloric if located within 3 cm of the pyloric ring; others were regarded as gastric. Cancer was excluded by biopsy.

Medical records were studied and patients were placed in three groups according to the type of operation: the three types of operation were simple closure, simple closure and vagotomy, and gastric resection. The mortality rate was calculated as death within 30 days of surgery.

All live patients were contacted for follow-up 1 to 11 years (mean 4·8 years) after operation.

The χ^2 test with Yates' correction was used for statistical analysis and *P*-values $<0{\cdot}05$ were considered significant.

Results

There were 139 men and 158 women (mean age 64·2 years, range 17–92 years). One hundred and fifty-five patients (52 per cent) had concurrent diseases making them more susceptible to postoperative complications and a higher mortality (*Table 1*). There was no history of peptic symptoms before perforation in 185 cases (62 per cent).

In 87 patients (29 per cent) the diagnosis of perforated ulcer was not considered at admission, the most frequent alternative diagnosis being intestinal obstruction (12 patients), appendicitis (6 patients), cholecystitis (7 patients) and no certain diagnosis (62 patients). Misdiagnosis, however, did not delay surgery. Ninety-one patients (31 per cent) had had perforation for > 24 h before surgery.

The locations of perforations are listed in *Table 2*. Gastric perforations were more frequent in women ($P<0{\cdot}001$) and prepyloric perforations in men ($P<0{\cdot}001$). Furthermore, gastric perforations were more common in patients $\geqslant 70$ years ($P<0{\cdot}05$) and prepyloric perforations in patients <50 years ($P<0{\cdot}01$).

Operation

Two hundred and forty-six patients (83 per cent, mean age 65·7 years) had simple closure and ten patients (3 per cent, mean age 63·6 years) simple closure and vagotomy. Gastric resection was performed in 41 patients (14 per cent, mean age 69·1 years). There were 221 postoperative complications in 161 patients (*Table 3*).

Table 1 *Number of patients in the three surgical groups with pre-operative concurrent diseases*

Main concurrent problem	Simple closure ($n=246$)	Simple closure ($n=10$)	Resection ($n=41$)
Cardiovascular	47 (12)	0	4 (4)
Respiratory	28 (6)	0	3 (2)
Diabetes mellitus	9 (4)	0	2 (0)
Malignancy	22 (13)	0	4 (0)
Multiple	11 (4)	0	4 (0)
Other	20 (4)	0	1 (1)
Total	137 (43)	0	18 (7)

Figures in parentheses refer to the number of deaths

Table 2 *Location of perforations in relation to patient age and sex*

	< 50 years		50–69 years		≥ 70 years		
Location	Male	Female	Male	Female	Male	Female	Total
Cardia	0	1	1	4	3	1	10
Gastric	9	11	18	36	25	47	146
Prepyloric	24	13	34	20	26	24	141
Total	33	25	53	60	54	72	297

Table 3 *Postoperative complications after surgery for perforated gastric ulcer (161 patients)*

Complication	Simple closure ($n=246$)	Simple closure and vagotomy ($n=10$)	Resection ($n=41$)
Reperforation	2	0	0
Ulcer bleeding	7 (2)	1	1
Septicaemia	21 (14)	1	5 (3)
Wound infection	41	2	10
Cardiovascular	59 (31)	1	6 (6)
Respiratory	41 (2)	2	13 (1)
Renal failure	8 (4)	0	0
Total	179 (53)	7	35 (10)

Figures in parentheses refer to the number of deaths

Mortality

The overall operative mortality rate was 21 per cent including 33 men and 30 women (mean age 72·6 years, range 45–93 years). Twenty-seven (43 per cent) of the fatalities had symptoms of perforation for > 24 h before operation and those patients with prolonged delay had significantly higher mortality ($P<0{\cdot}05$). A higher mortality rate was also found among patients > 70 years (42 patients *versus* 21, $P<0{\cdot}001$) as well as in patients with concurrent diseases (50 patients *versus* 13, $P<0{\cdot}001$). Although the mortality rate was higher among patients who underwent resection, this difference was not statistically significant. The main causes of death are listed in *Table 3*.

Follow-up

Of 234 patients who left hospital, information was obtainable in 170 (73 per cent). Seventy-two patients had died from causes unrelated to their ulcer disease. Forty-four patients treated with simple closure and simple closure and vagotomy were asymptomatic. Four had died from reperforation and three from haematemesis. Thirty-two had recurrent symptoms and ten of these patients had undergone reoperation. Among patients undergoing gastric resection, five had no symptoms, two had died from reperforation and bleeding ulcer respectively and eight had recurrent discomfort but only one had come to reoperation.

Discussion

Throughout this century there has been a steady change in age and sex distribution of patients with perforated peptic ulcer of the stomach. The former preponderance in males has been almost equalized and average age has increased in both sexes[2–5]. Our study confirms that patients with perforated gastric ulcers are often elderly and that the location of perforation is influenced by age and sex. Gastric ulcer perforation occurred predominantly in the elderly female patient whereas prepyloric ulcer perforation was more common in the younger male than in female and elderly male patients.

The surgical treatment of perforated peptic ulcer is still a matter of debate. Since Graham[6] published his method of simple closure with an omental patch, this has been adopted as a safe procedure, especially when dealing with poor risk patients where more major surgery is unwarranted during the acute phase[7–9]. However, complications such as reperforation and postoperative ulcer bleeding, the risk of missing a gastric carcinoma and the fact that no definitive treatment of the peptic disease was undertaken have made others advocate partial gastrectomy[10,11]. Collier and Pain[5] claimed that gastric resection is an unnecessarily extensive procedure as many patients remained without symptoms after simple closure. It has been suggested that gastric resection should be reserved for those patients with long-standing peptic ulcer disease which has not responded to H_2-receptor antagonists.

In our series simple closure with biopsy was the commonest treatment. This may partly reflect the high number of poor risk patients and the fact that 62 per cent had no history of peptic disease before perforation. In view of the high frequency of pre-operative concurrent diseases, the number of postoperative complications are comparable to other reports[8,11,12].

The recorded mortality rates from perforated gastric ulcer differ considerably[8,10,12]. We found age, pre-operative condition of the patients and delay in surgery to be primary determinants of survival. Almost one-third of the patients was misdiagnosed, but the delay in surgery was related to late admission rather than uncertain or erroneous diagnosis at time of operation. The choice of surgical procedure did not seem to influence the outcome.

The high mean age at operation reduced the number of patients available for personal contact at follow-up. Among 76 survivors treated with an omental patch 44 (58 per cent) were asymptomatic. This is a better result than usually reported[8,10,12], but may be explained by the short observation time.

We recognize that it is difficult to compare complications and mortality in a study where patients are not matched. The outcome, however, makes us recommend biopsy and simple closure for benign perforated gastric ulcer when technically feasible. Gastric resection should be reserved for patients with chronic ulcers resistant to medical treatment.

References

1. Sanders R. Incidence of perforated duodenal and gastric ulcer in Oxford. *Gut* 1967; **8**: 58–63.
2. Brown RC, Langman MJS, Lambert PM. Hospital admission for peptic ulcer during 1958–1972. *Br Med J* 1976; **i**: 35–7.
3. Walt R, Katschinski B, Logan R, Ashley J, Langman M. Rising frequency of ulcer perforation in elderly people in the United Kingdom. *Lancet* 1986; **i**: 489—92.
4. Watking RM, Dennison AR, Collin J. What has happened to perforated peptic ulcer? *Br J Surg* 1984; **71**: 774–6.
5. Collier DStJ, Pain JA. Perforated gastric ulcer. *J R Coll Surg Edinb* 1985; **30**: 26–9.
6. Graham RR. The treatment of perforated duodenal ulcers. *Surg Gynecol Obstet* 1937; **64**: 235–8.
7. Cohen MM. Treatment and mortality of perforated peptic ulcer: a survey of 852 cases. *Can Med Assoc J* 1971; **105**: 263–9.
8. Jordan GL, DeBakey ME, Duncan JM. Surgical management of perforated peptic ulcer. *Ann Surg* 1974; **179**: 628–33.
9. Van Hee R. Results of simple suture for perforated peptic ulcer. *Acta Chir Belg* 1984; **84**: 97–102.
10. Olsen AK, Liavag I, Roland M. Ulcus perforatum. *Tidsskr Nor Laegeforen* 1983; **28**: 1924–7.
11. Feliciano DV, Bitondo CG, Burch JM, Mattox KL, Jordan GL, DeBakey ME. Emergency management of perforated peptic ulcers in the elderly patient. *Am J Surg* 1984; **148**: 764–7.
12. Donaldson GA, Jarrett F. Perforated gastroduodenal ulcer disease at the Massachusetts General Hospital from 1952 to 1970. *Am J Surg* 1970; **120**: 306–11.

Paper accepted 1 April 1988

Br. J. Surg. 1988, Vol. 75, August, 760–763

Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus

C. S. Robertson, J. F. Mayberry, D. A. Nicholson, P. D. James* and M. Atkinson

Department of Surgery and
**Department of Histopathology,*
Queen's Medical Centre,
Nottingham NG7 2UH, UK

Correspondence to:
Professor M. Atkinson

Fifty-six patients with Barrett's oesophagus diagnosed between 1977 and 1986 were prospectively studied by 6-monthly endoscopic surveillance and biopsy. During follow-up to-date, four patients have developed high-grade dysplasia and three have adenocarcinoma of the oesophagus. Two of the adenocarcinomas were preceded by progressively severe dysplastic changes but in the third no dysplasia had been previously detected. The incidence of adenocarcinoma was 1 per 56 patient-years of follow-up. Changes in symptomatology or gross endoscopic appearances were usually absent, even after adenocarcinoma had developed, indicating that biopsy is essential for early diagnosis. The high risk of malignant change makes endoscopic surveillance advisable in all patients with Barrett's oesophagus.

Keywords: Barrett's oesophagus, carcinoma of the oesophagus, gastro-oesophageal reflux, endoscopic surveillance

It is generally accepted that Barrett's columnar epithelial-lined oesophagus[1] is the result of severe, prolonged gastro-oesophageal reflux[2], and that it carries a risk of adenocarcinomatous change[3]. Widely differing estimates of the magnitude of this risk have been made, and this may, in part, be because of some having been based on prevalence[4] rather than incidence data. Prevalence studies include patients presenting with adenocarcinoma, and have been criticized for tending to exaggerate the risk of malignancy[5].

Epithelial dysplasia frequently accompanies invasive adenocarcinoma and is regarded as a precursor of adenocarcinoma[6]. Additional evidence to support this close association is the recent demonstration of aneuploidy in dysplasia and adenocarcinoma associated with Barrett's oesophagus[7]. However, the significance of dysplasia in terms of clinical management is still uncertain as the rate of progression to malignancy is not clear.

To help clarify these problems we report the findings of a 10-year prospective endoscopic survey involving 56 patients with Barrett's oesophagus.

Patients and methods

Between 1977 and 1986, 56 consecutive patients with a diagnosis of Barrett's columnar epithelial-lined oesophagus were entered into a follow-up programme of endoscopic surveillance with multiple biopsies approximately twice yearly. Those in whom a carcinoma was present at first examination were excluded from the study. The diagnosis was made when the columnar mucosa extended circumferentially up the oesophagus for 5 cm or more from the oesophagogastric junction which was defined endoscopically. At each examination the level of the squamocolumnar junction was measured from the incisor teeth, and the presence of hiatus hernia, oesophagitis, oesophageal ulcer or stricture was noted. In addition, up to six random biopsies were taken from the columnar-lined oesophagus using endoscopic biopsy forceps (Olympus FB 13K).

Biopsies from the 56 patients were examined by one histopathologist (P.D.J.); the origin of each biopsy was known, and earlier and subsequent biopsies were available for comparison. No attempt was made to assess observer error. Specimens were fixed in neutral buffered formalin, routinely processed to paraffin, and multiple sections from each block were stained using haematoxylin and eosin, Alcian Blue pH 2·5/periodic acid Schiff, and high iron diamine/Alcian Blue pH 2·5. Each biopsy was examined for the histological type of epithelium present[8], the presence and type of intestinal metaplasia[9], for sulphomucin secretion, and for dysplasia or carcinoma.

A system for grading dysplasia in inflammatory bowel disease has been proposed[10] and this has been applied to Barrett's oesophagus[4,5,11]. The nomenclature used in the classification of the epithelial changes is shown in *Table 1*. Dysplasia is defined as an unequivocal neoplastic alteration in the columnar mucosa which is distinguishable from reactive or regenerative abnormalities[10]. When a definite distinction is not possible, the changes are categorized as indefinite for dysplasia. Dysplasia is characterized by pleomorphism and hyperchromatism of nuclei with loss of nuclear polarity. In high-grade dysplasia there are pronounced nuclear changes: loss of normal basal polarity of the nuclei with marked pseudostratification. The interpretation of dysplastic changes is, at present, subjective but comparative studies have shown that an experienced pathologist can distinguish high-grade dysplasia from other lesions[12,13].

Results

Of the 56 patients studied, 31 were men, and the mean age at diagnosis was 62 years (range 23–84). The mean follow-up period was 35 months (range 6–108 months); four patients, all women, died during follow-up from unrelated causes. The chief presenting symptoms were heartburn, acid reflux and dysphagia (*Table 2*). Alcohol and tobacco consumption were no greater than in a control group of patients attending the fracture clinic (*Table 3*). At endoscopy, 47 (84 per cent) had histologically confirmed oesophagitis in the squamous-lined oesophagus, 46 (82 per cent) had a hiatus hernia, 29 (52 per cent) had chronic peptic ulcer in the columnar-lined segment, and 23 (41 per cent)

Table 1 *Classification of dysplasia in Barrett's epithelium*

Negative for dysplasia

Indefinite for dysplasia
- Probably negative
- Unknown significance
- Probably positive

Positive for dysplasia
- Low grade
- High grade

Table 2 *Clinical features in 56 patients with Barrett's oesophagus*

Symptoms	Number of patients	%
Heartburn	39	70
Dysphagia	31	55
Acid reflux	29	52

Mean duration of symptoms (± s.d.) was 5·5 ± 2·3 years

0007–1323/88/080760–04$3.00

had a benign peptic stricture. All patients received long-term treatment with H_2-receptor blocking drugs after diagnosis; treatment with H_2-antagonists was variable before diagnosis. During the follow-up period, the columnar mucosa in 11 patients (20 per cent) progressed up the oesophagus by as much as 6 cm (*Figure 1*) in spite of continuing H_2-receptor blocker therapy. In no patient did regression of the columnar lining occur, nor has the squamocolumnar junction regressed in the four patients who had a surgical antireflux procedure.

The mucosal type present in 162 biopsies of benign columnar epithelium is shown in *Table 4*. A mixture of junctional (cardiac) and specialized (intestinal) epithelium was found in 40 patients, with junctional or specialized mucosa occurring alone in most of the remainder. Specialized mucosa alone or with another type was found in 105 (65 per cent) biopsies, and sulphomucin secretion was present in 94. Intestinal metaplasia and sulphomucin secretion were both present in at least 1 biopsy from 43 (78 per cent) of the 55 patients studied.

Table 3 *Social habits of patients with Barrett's oesophagus and an age and sex matched group of patients attending the fracture clinic*

	Barrett's oesophagus ($n=40$)	Control patients ($n=40$)
Non-smokers	24	26
Smokers		
Pipe/cigar	2	0
≤10 cigarettes/day	7	10
>10 cigarettes/day	7	4
Non-drinkers	19	17
Median weekly alcohol intake (g)	40 (0–120)	60 (0–234)

Interquartile range is given in parentheses

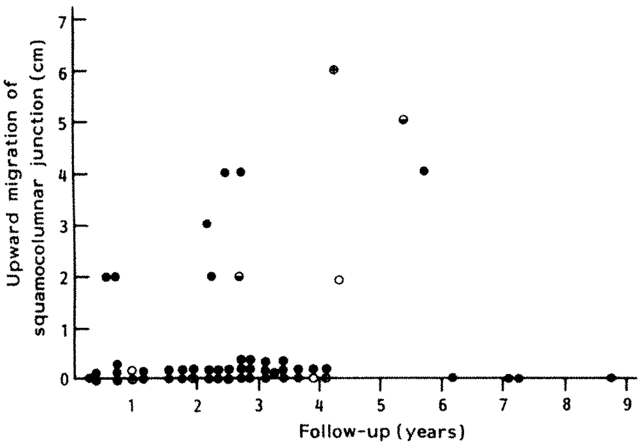


Figure 1 *Upward progression of the squamocolumnar epithelial junction as measured from the incisor teeth at endoscopy.* ●, *Patients without dysplasia;* ⊕, *patients with dysplasia;* ◒, *patients with severe dysplasia;* ○, *patients with adenocarcinoma*

Dysplasia classified as indefinite probably negative was present in eight biopsies from four patients, but in two this was absent in later biopsies. In four patients (all men) severe dysplasia occurred during the study period: specialized epithelium with sulphomucin secretion had been found on earlier biopsies in each patient. Adenocarcinoma subsequently developed in two of these after intervals of 11 and 14 months respectively (*Figure 2*). Adenocarcinoma developed in a third patient in whom previous biopsies had not shown any dysplasia. Progression of the gastric epithelium up the oesophagus was not associated with an increased risk of malignant change; only 1 of the 11 patients developed an invasive adenocarcinoma (95 per cent confidence limits 0–5) compared with 2 of 45 (95 per cent confidence limits 0–7) ($z=0{\cdot}13$; $P=$n.s.[14]; *Figure 1*). There was no change in the symptoms of those patients who developed neoplastic change and, from gross endoscopic appearances, carcinoma was identified in only one of the three cases in which malignancy was demonstrated histologically, the other two cases being picked up on random biopsy.

Seven patients have had surgical treatment: four uncomplicated cases, with no dysplasia, had an antireflux procedure; and three patients had an Ivor–Lewis oesophagectomy, two with carcinoma and one with severe dysplasia. All are currently alive and well.

One of our patients who developed adenocarcinoma, because of infirmity and co-existent carcinoma of the prostate, has had

Table 4 *Histological type of epithelium in 162 biopsies from 55 patients with Barrett's oesophagus*

	Number of biopsies
One type of mucosa only	
Junctional (J)	49 (30)
Fundal (F)	4
Specialized (intestinal) (S)	23 (14)
More than one type	
J + F	4
J + S	80 (49)
J + F + S	1
S + F	1

Values in parentheses are percentages

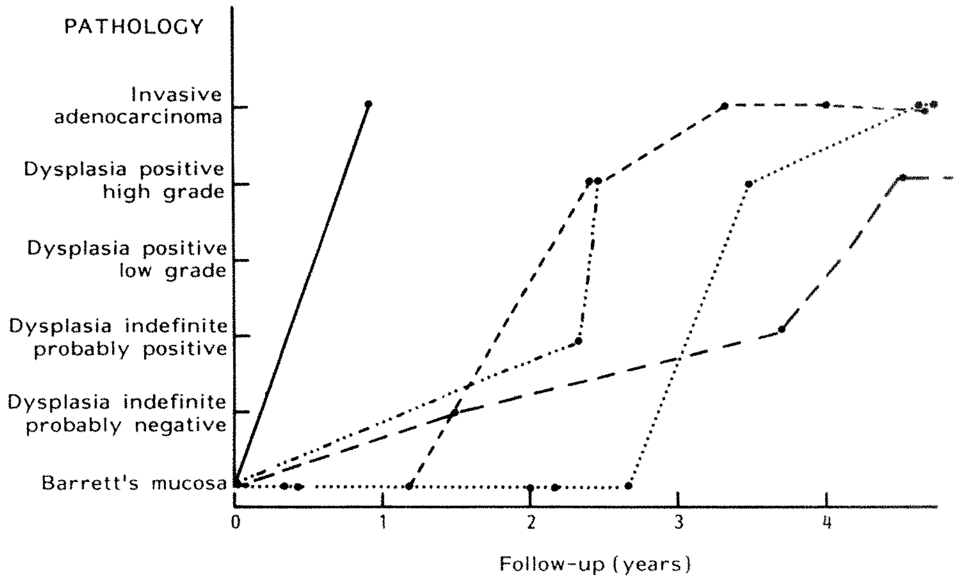


Figure 2 *Procession of pathological changes during follow-up in five patients with severe dysplasia and/or adenocarcinoma*

no specific treatment. However, he has now survived 3 years since the initial diagnosis of malignancy and currently has only mild dysphagia with no weight loss. This highlights a problem in these patients in that the rate of progression of malignant change may be slow and exceed the life expectancy of elderly patients.

Discussion

The marked heterogeneity of the mucosa in Barrett's oesophagus is well recognized[8,15,16], and our findings correspond with those in a recently reported series from this country[17]. A mixture of junctional and specialized epithelium is the commonest mucosal type, found in nearly half of our mucosal biopsies. A single mucosal type of either junctional or specialized epithelium was present in most of the remaining biopsies, with other mucosal types occurring infrequently.

Intestinal metaplasia, mucin histochemistry, and the risk of the subsequent development of gastric carcinoma have been reviewed[9]. The mucin histochemistry of Barrett's mucosa has been studied[6,17–20], and these reports show that incomplete intestinal metaplasia and sulphmucin secretion are common features of the columnar-lined oesophagus. In the present study, intestinal metaplasia and sulphomucin secretion were found in 65 per cent and 58 per cent of biopsies respectively, both being present in at least one biopsy from 78 per cent of the patients studied. We would agree with the conclusions of others that sulphomucin secretion is a common occurrence and is not a sufficiently sensitive marker to predict those patients at risk of developing adenocarcinomas[17]. However, the five patients who developed dysplasia or adenocarcinoma all demonstrated specialized epithelium and sulphomucin secretion in earlier biopsies.

Estimates of the risk of malignant change in Barrett's oesophagus vary greatly. The incidence of cancer amongst our 56 patients with Barrett's oesophagus was 1786 per 10^5 patients per year, or 1 per 56·0 patient-years of follow-up. Because of the difficulty in determining whether adenocarcinoma involving the lower oesophagus has arisen in the stomach, comparative figures for the incidence in the general population are not available. However, the incidence of squamous carcinoma of the oesophagus has been reported to be 5·1 per 10^5 patients per year[21] which indicates that in Barrett's oesophagus the risk of oesophageal cancer is increased 350 times (95 per cent confidence limits 139–960). It may be more appropriate to compare the incidence of adenocarcinoma in Barrett's oesophagus with that of gastric cancer which is 28·8 per 10^5 patients per year[22]. Even so, the relative risk remains significantly elevated at 62 times (95 per cent confidence limits 42–91). There was no significant difference in cancer risk between men and women (Fisher's exact test[14]).

In contrast, in two studies from New Zealand no malignant change occurred. In the first, 45 patients identified incidentally during a study of hiatus hernia followed for up to 22 years remained free of cancer[23], and in the second[24] 52 patients with Barrett's oesophagus were followed up for a mean period of 16·9 months. However, Cameron *et al.*[25] reported the development of carcinoma in 2 of 102 patients with columnar-lined oesophagus, identified between 1961 and 1979, giving an incidence of 1 case per 441 patient-years. In a series of 105 patients, Spechler *et al.*[26] reported that 2 developed carcinoma, with a rate of 1 per 175 patient-years, which was a 40-fold higher risk than in the American general population. This study included some patients with very limited involvement of the oesophagus, and the group was almost exclusively male; 85 per cent were smokers and 76 per cent had evidence of heavy alcohol consumption, leading the authors to speculate that the high incidence of cancer was related to these factors. We were unable to confirm this in the present study.

Barrett's oesophagus is clearly a premalignant condition. In a group of 56 patients we would expect at least 1 to develop carcinoma each year. Particular risk factors are difficult to identify, and in this study the rate of extension of the squamocolumnar junction up the oesophagus was not associated with an increased risk of malignant change. Neither symptomatic response to continued active medical treatment for gastro-oesophageal reflux nor the consumption of alcohol and tobacco appeared to have any obvious prognostic significance.

There was no selection bias in this group of patients and—apart from the fact that columnar epithelialization of the oesophagus was extensive (≥5 cm), that complications were common, and that a smaller number of patients were involved than in the two American incidence studies[25,26]—we have no satisfactory explanation for our high incidence of malignant change.

At present, dysplasia appears to be the only reliable morphological marker for adenocarcinoma[6,17], although flow cytometry and nuclear aneuploidy may be helpful in detecting patients at risk[7]. In one of our three patients who developed adenocarcinoma, oesophageal biopsies had been obtained on only one previous occasion and had not then shown dysplastic change; in general, however, progressive increase in severity of dysplastic change occurred with time and was noted in the other two patients in whom malignant change occurred. The imminence of neoplastic change in the presence of dysplasia is difficult to predict; in two of our patients, adenocarcinoma developed 11 and 14 months, respectively, after high-grade dysplasia was first noted. Lee[6] reported four patients with severe dysplasia arising in columnar-lined oesophagus; in three patients adenocarcinoma developed within a period of 7–38 months. Until more sensitive methods are available, dysplasia remains the only reliable marker for the detection of patients with Barrett's oesophagus at risk of developing subsequent malignancy.

The present study emphasizes the importance of obtaining adequate material for histology at both endoscopy and at operation. Our findings indicate that gross changes of neoplasm are often lacking in patients with adenocarcinoma; this leads to difficulties in endoscopic diagnosis, and in the determination of the extent of the growth at surgery, when frozen sections should be taken to ensure resection of all the columnar-lined oesophagus.

Prospective endoscopic surveillance for the detection of increasing dysplasia and malignant change, although expensive and time consuming, would appear to be well worthwhile in Barrett's oesophagus in view of the high risk of adenocarcinoma. The mean age of our patients at the time of entry to follow-up was 62 years, which is considerably less than that for squamous carcinoma of the oesophagus. Hence the early detection of actual or impending neoplastic change is particularly important in patients with Barrett's oesophagus because they are more likely to be fit enough to undergo surgical resection.

We therefore suggest annual endoscopy with biopsy. Patients with severe dysplasia should be offered oesophageal resection, and those with lesser degrees of dysplasia must be kept under careful review.

References

1. Barrett R. Chronic peptic ulcer of the oesophagus and oesophagitis. *Br J Surg* 1950; **38**: 175–82.
2. Winters C, Spurling TJ, Chobanian SJ *et al.* Barrett's oesophagus—a prevalent occult complication of gastro-oesophageal reflux. *Gastroenterology* 1987; **92**: 118–24.
3. Naef AP, Savary M, Ozzello L. Columnar-lined lower oesophagus: an acquired lesion with malignant predisposition. *J Thorac Cardiovasc Surg* 1975; **70**: 826–34.
4. Skinner DB, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus. Comparison of benign and malignant cases. *Ann Surg* 1983; **198**: 554–65.
5. Spechler SJ, Goyal RK. Barrett's esophagus. *N Engl J Med* 1986; **315**: 362–71.
6. Lee RG. Dysplasia in Barrett's esophagus. A clinicopathological study of six patients. *Am J Surg Path* 1985; **9**: 845–52.

7. Reid BJ, Haggitt RC, Rubin CE, Rabinovitch PS. Barrett's esophagus. Correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. *Gastroenterology* 1987; **93**: 1–11.
8. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's oesophagus. *N Engl J Med* 1976; **295**: 476–80.
9. Filipe MI, Jass JR. Intestinal metaplasia subtypes and cancer risk. In: Filipe MI, Jass JR, eds. *Gastric carcinoma*. Edinburgh: Churchill Livingstone, 1986.
10. Riddell RH, Goldman H, Ransohoff DF *et al*. Dysplasia in inflammatory bowel disease: standard classification with provisional clinical applications. *Human Pathology* 1983; **14**: 931–68.
11. Hamilton SR, Smith RL. The relationship between columnar epithelial dysplasia and invasive adenocarcinoma arising in Barrett's esophagus. *Am J Clin Pathol* 1987; **87**: 301–12.
12. Reid BJ, Haggitt RC, Rubin CE *et al*. Criteria for dysplasia in Barrett's esophagus: a co-operative consensus study. *Gastroenterology* 1985; **88**: 1552.
13. Dundas SAC, Kay R, Beck S *et al*. Can histopathologists reliably assess dysplasia in chronic inflammatory bowel disease? *J Clin Path* 1987; **40**: 1282–6.
14. Siegel S. *Non-parametric Statistics for the Behavioural Sciences*. Tokyo: McGraw-Hill, Kogakusna Ltd, 1956.
15. Ozzello L, Savary M, Roethlisberger B. Columnar mucosa of the distal esophagus in patients with gastroesophageal reflux. *Pathology Annual* 1977; **12**: 41–86.
16. Thompson JJ, Zinsser KR, Enterline HT. Barrett's metaplasia and adenocarcinoma of the esophagus and gastroesophageal junction. *Human Pathology* 1983; **14**: 46–61.
17. Rothery GA, Patterson JE, Stoddard CJ, Day DW. Histological and histochemical changes in the columnar lined (Barrett's) oesophagus. *Gut* 1986; **27**: 1062–8.
18. Jass JR. Mucin histochemistry of the columnar epithelium of the oesophagus: a retrospective study. *J Clin Path* 1981; **34**: 866–70.
19. Sheahan DG, West AB. Sulfated mucosubstances in Barrett's (columnar cell) esophageal mucosa. *Gastroenterology* 1981; **80**: 1282.
20. Peuchmaur M, Potet F, Goldfain D. Mucin histochemistry of the columnar epithelium of oesophagus (Barrett's oesophagus): a prospective biopsy study. *J Clin Path* 1984; **37**: 607–10.
21. Doll R, Muir C, Waterhouse J. *Cancer Incidence in Five Continents*, Vol. 1. Berlin: Springer Verlag, 1900.
22. Langman MJ. *The Epidemiology of Chronic Digestive Disease*. Chicago: Year Book Medical Publishers, 1986.
23. Borrie J, Goldwater L. Columnar cell lined oesophagus: assessment of etiology and treatment—a 22 year experience. *J Thorac Cardiovasc Surg* 1976; **71**: 825–30.
24. Cooper BT, Barbezat GO. Barrett's oesophagus: a clinical study of 52 patients. *Q J Med* 1987; **62**: 97–108.
25. Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in a columnar-lined (Barrett's) esophagus. *N Engl J Med* 1985; **313**: 857–9.
26. Spechler SJ, Robbins AH, Rubins HB *et al*. Adenocarcinoma and Barrett's esophagus. An over-rated risk? *Gastroenterology* 1984; **87**: 927–33.

Paper accepted 10 April 1988

Change of address

Please note that from 13 June 1988 the editorial office is moving to Butterworth Scientific Ltd.
Please send all correspondence to:

Lynne Ponjee,
Editorial Secretary,
Butterworth Scientific Ltd.,
PO Box 63, Westbury House,
Bury Street, Guildford,
Surrey GU2 5BH, UK
Telephone: 0483 301439

Br. J. Surg. 1988, Vol. 75, August, 764–766

Enucleated parotid tumours

J. D. Maynard

Gordon Museum, Guy's Hospital, London SE1 9RT, UK

Correspondence to:
Mr J. D. Maynard

Five pleomorphic, one monomorphic adenoma and one acinic cell lower pole parotid tumours were thought to be lymph nodes and enucleated. Wide excision of the operative site within 2 months revealed microscopic recurrence in three cases. Three carcinomas were enucleated and two had recurred rapidly. It is suggested that such cases of inadvertent enucleation should undergo wide resection of the operative site with nerve dissection.

Keywords: Frequent recurrence, early reoperation, pleomorphic adenoma

Occasionally a tumour in the lower pole of the parotid gland is mistaken for an enlarged lymph node and is excised or enucleated through a small incision (*Figure 1*). This is more likely to occur in younger patients in whom parotid neoplasms are particularly rare. Occasionally the histology reveals a carcinoma and most surgeons would then suggest further surgery or radiotherapy. More commonly the neoplasm is a pleomorphic adenoma, very occasionally a low grade muco-epidermoid or acinic cell tumour. The question of further surgery with concomitant risk to the facial nerve, or radiotherapy with its own complications particularly in the young, must be weighed against the undoubted risk of recurrence. Benign neoplasms such as adenolymphomas need no further treatment.

A policy of immediate further surgical treatment of enucleated pleomorphic adenomas, acinic cell tumours and low grade muco-epidermoid tumours[1] was started 13 years ago.

Patients and methods

Ten patients who, inadvertently, had had inadequate surgery were referred in the last 13 years. In this personal series a routine wide excision of the site of the previous surgery was performed after dissection of the facial nerve[2]. The scar of the previous surgery was widely excised in continuity with the deeper tissues. As might be expected the recurrence rate in the three carcinomas was high (*Table 1*). The high grade muco-epidermoid tumour developed a probable recurrence within 1 month of the original enucleation and was treated elsewhere with a full course of radiotherapy. During treatment the probable recurrence appeared to increase in size. A radical parotidectomy and nerve graft, together with wide excision of the overlying skin followed biopsy and frozen section confirming the recurrence.

The patient with a squamous cell carcinoma underwent enucleation of the tumour followed by a radium implant and developed a haematoma which failed to resolve. Malignant cells were found in the saliva from the parotid and a radical parotidectomy and nerve graft was carried out (*Table 1*).

Of the seven patients with benign tumours or a low grade carcinoma, who all underwent reoperation within 2 months of their previous surgery, no fewer than three had already developed microscopic recurrent tumour (*Table 1*). The recurrences had developed in the scar tissue in the parotid gland at the site of the previous surgery and were multicentric in the pleomorphic adenomas (*Figures 2* and *3*) and solitary in the patient with the acinic cell tumour (*Figure 4*).

One patient was lost to follow-up and there were no cases of further recurrence of tumour in the 13-year period, with the exception of the patient with the adenocarcinoma. He developed a recurrent tumour in the buccal fat on the same side as his original tumour 4 years later. It was widely excised and he is currently undergoing radiotherapy. Among the seven patients with pleomorphic and acinic cell tumours two cases developed mild Frey's syndrome and there was a slight but obvious weakness of the lower lip in one patient. This has remained unchanged for 9 years.

Of the three patients with carcinoma there was no recovery of facial nerve function in two patients. The boy with a muco-epidermoid carcinoma underwent a near-total parotidectomy and block dissection but the main trunk and upper division of the facial nerve were spared and the lower main division grafted. He now has weakness only of the lower lip.

Discussion

Slow-growing parotid tumours frequently expand into the lower pole of the gland. Occasionally they extend below the lower pole of the parotid and may be considered on clinical examination to be unrelated to the parotid (*Figure 1*) and to be enlarged lymph nodes. As parotid tumours are rare in children and enlarged nodes not uncommon, it is not surprising that half this series is aged under 25 and nearly a third 15 years or less.

On the rare occasions when inadequate surgery is performed inadvertently for malignant parotid tumours, most surgeons would agree that further surgery is indicated. In the three cases described here two had already recurred, one within 2 months, and it would seem that further surgery is justified.

The dilemma of whether of not to advise further surgery for inadvertently enucleated pleomorphic adenomas and the rare acinic cell and muco-epidermoid tumours has been difficult to resolve. In personal discussion some colleagues have taken the view that the risk of recurrence is slight in comparison to the risk of facial nerve damage and that the situation could be salvaged by further surgery if, after careful follow-up, a recurrence occurs.

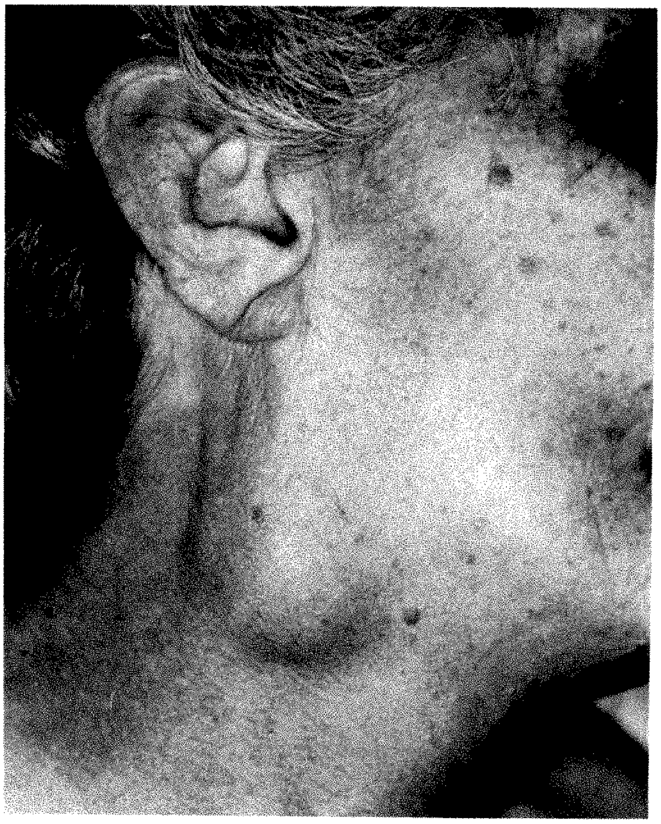


Figure 1 *Adenolymphoma treated by wide excision*

0007–1323/88/080764–03$3.00

Table 1 *Enucleated parotid neoplasms with wide excision of operation site*

Neoplasm	Age and sex	Interval between operations	Findings	Follow-up	Complications
Carcinomas					
1. Adenocarcinoma	54 M	1 month	No recurrent tumour	4 years: recent recurrence. Excised and radiotherapy	Complete facial palsy
2. Muco-epidermoid carcinoma	13 M	2 months	Recurrent tumour	4 years: no recurrence	Weakness of lower lip
3. Squamous cell carcinoma	68 M	11 months	Recurrent tumour	7 years: died, no recurrence	Complete facial palsy
Pleomorphic and monomorphic adenomas and acinic cell tumour					
4. Pleomorphic adenoma	15 M	1 month	No recurrent tumour	13 years: no recurrence	Frey's syndrome
5. Pleomorphic adenoma	19 F	2 months	No recurrent tumour	Lost to follow up	—
6. Pleomorphic adenoma	36 M	5 weeks	No recurrent tumour	3 years: no recurrence	—
7. Monomorphic adenoma	41 M	2 weeks	No recurrent tumour	5 years: no recurrence	—
8. Pleomorphic adenoma	15 F	1 month	Microscopic recurrent tumour	9 years: no recurrence	Slight weakness of lower lip
9. Pleomorphic adenoma	23 F	1 month	Microscopic recurrent tumour	6 years: no recurrence	Frey's syndrome
10. Acinic cell tumour	42 M	1 month	Microscopic recurrent tumour	6 years: no recurrence	—

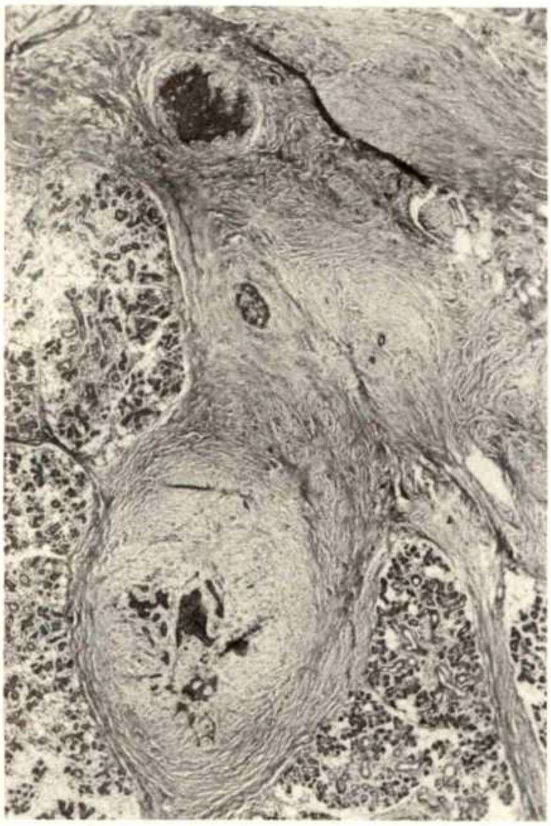


Figure 2 *Case 8: haematoxylin and eosin stained preparation showing multifocal recurrent pleomorphic adenoma (magnification × 38)*

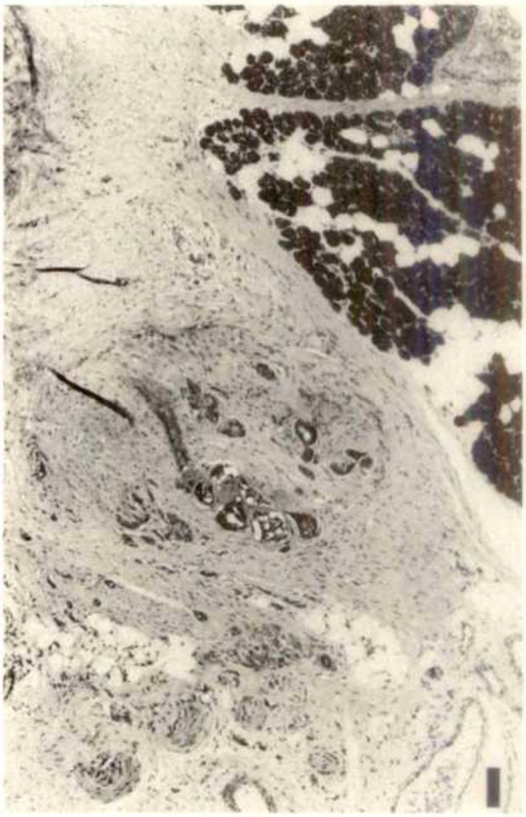


Figure 3 *Case 9: haematoxylin and eosin stained preparation showing multifocal recurrent pleomorphic adenoma (graticule ≡ 100 μm)*

Others have attempted to minimize the risk of recurrence by advising postoperative radiotherapy.

Before 1950 all pleomorphic adenomas were enucleated. Often this meant a small incision over the tumour and aspiration of the contents. It is common knowledge that the recurrence rate after such a procedure was high. As long ago as 1941, Bailey[3] had recommended that the capsule must be excised as well because of the high recurrence rate after aspiration alone. After short follow-up periods McEvedy[4] reported in 1934 a 20 per cent recurrence rate after 'enucleation'. Two years later McFarland[5] reported a 21·5 per cent recurrence rate in 278 similar cases. Patey[6] discussed the high recurrence rate after enucleation and Smiddy[7] reported no fewer than 16 recurrence in 19 similar cases. Wyatt and Henry[8] and Maimaris and Ball[9] in retrospective surveys recently reported 10 per cent and 12 per cent recurrence rates, respectively.

However, if the enucleation is a meticulous extra-capsular dissection the recurrence rate is the same as wide excision with dissection of the facial nerve as described in one large series[10]. It is probable that enucleation of a suspected lymph node is not performed with such meticulous extra-capsular dissection.

If a policy of no further surgery and follow-up is adopted, certain other factors should be taken into consideration if recurrence does occur. Recurrences are frequently multifocal and may involve branches of the facial nerve necessitating sacrifice of all or part of the nerve if further recurrence is to be avoided. Further recurrence after surgery for recurrence is not uncommon with increased risk to the facial nerve. Malignant

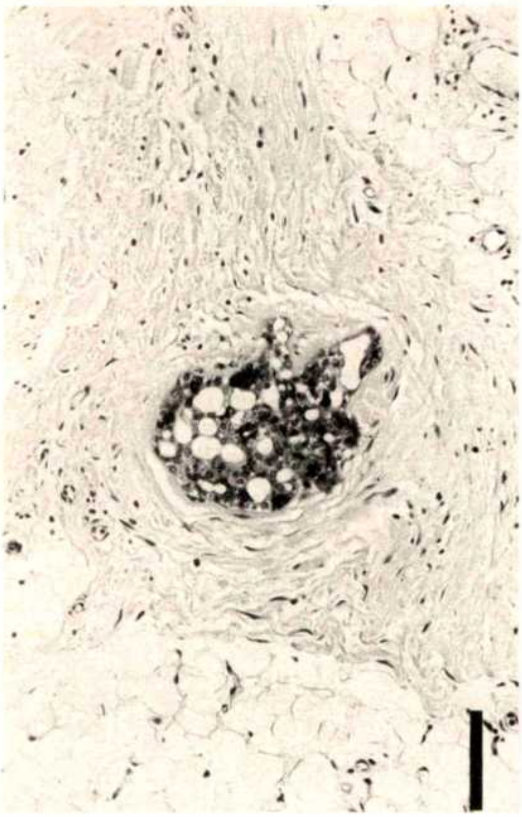


Figure 4 *Case 10: haematoxylin and eosin stained preparation showing recurrent acinic cell tumour (graticule ≡ 100 μm)*

change in pleomorphic adenomas occurs after usually long periods of growth but sometimes more quickly. Slow-growing acinic cell and muco-epidermoid tumours may metastasize. All these tumours grow slowly and late recurrence is common. Patients frequently fail to attend follow-up appointments after several years. Once they have escaped from supervision patients fail to notice the presence of a recurrence sometimes for many years, particularly if the recurrence is not superficial[11]. Occasionally the first symptom of recurrence is pain or facial palsy, which indicates the transformation of the occult recurrence into a malignant pleomorphic adenoma or infiltration by an acinic cell or muco-epidermoid tumour.

Prophylactic radiotherapy is of dubious value in salvaging inadequate surgery for these tumours. Watkin and Hobsley[12] have recently suggested that radiotherapy after local excision did not affect the interval between operation and recurrence. More important is the long-term effect of radiotherapy and the possibility of inducing further parotid neoplasia in the future[13]. Children are particularly vulnerable in this respect[14,15]. It is probable that misdiagnosis of parotid tumours is more common in children and irradiation as a measure of prophylaxis should not be considered. Cranial nerve damage occasionally develops as a complication of radiotherapy[16].

In this small collection of enucleated pleomorphic and monomorphic adenomas and one acinic cell tumour, no fewer than three out of seven had recurred microscopically within 1 month of the original surgery. It is suggested that the best management of these problems in the future should be to treat the operation site and the operation scar as an existing neoplasm and to carry out a wide excision after dissection of the facial nerve.

References

1. Taylor S, Chisholm GD, O'Higgins N, Shields R. *Surgical Management*, 1st edn. London: Heinemann, 1984: 678–92.
2. Maynard JD. Submandibular and parotid gland resection. *Br J Hosp Med* 1978; **20**: 70–9.
3. Bailey H. The treatment of tumours of the parotid gland. *Br J Surg* 1941; **28**: 337–46.
4. McEvedy PG. Diseases of the salivary gland. *Clin J* 1934; **63**: 334–8.
5. McFarland J. 300 mixed tumours of salivary glands of which 69 recurred. *Surg Gynecol Obstet* 1936; **63**: 457–68.
6. Patey DH. The treatment of mixed tumours of the parotid gland. *Br J Surg* 1940; **28**: 29–38.
7. Smiddy FS. Treatment of mixed parotid tumours. *B Med J* 1956; **1**: 322–5.
8. Wyatt AP, Henry L, Curwen MP. Salivary tumours. *Br J Surg* 1967; **54**: 636–45.
9. Maimaris CV, Ball MJ. The treatment of parotid gland tumours by conservative parotidectomy. *Br J Surg* 1986; **73**: 897–8.
10. Gleave EN, Whittaker JS, Nicholson A. Salivary tumours, experience over 30 years. *Clin Otol* 1979; **4**: 247–57.
11. Eddey HH. Recurrent parotid tumours. *Aust NZ J Surg* 1970; **39**: 356–61.
12. Watkin GT, Hobsley M. Influence of local surgery and radiotherapy on the natural history of pleomorphic adenomas. *Br J Surg* 1986; **73**: 74–6.
13. Watkin GT, Hobsley M. Should radiotherapy be used routinely in the management of benign parotid tumours? *Br J Surg* 1986; **73**: 601–3.
14. Modan B, Baidatz D, Mart H, Steinitz R, Levin SG. Radiation-induced head and neck tumours. *Lancet* 1974; **i**: 277–9.
15. Schneider AB, Favus MJ, Stachura ME, Arnold MJ, Frohman LA. Salivary gland neoplasms as a late consequence of head and neck irradiation. *Am Intern Med* 1977; **87**: 160–4.
16. Berger PS, Bataini JP. Radiation-induced cranial nerve palsy. *Cancer* 1977; **40**: 152–5.

Paper accepted 29 March 1988

Br. J. Surg. 1988, Vol. 75, August,
767–769

Use of older patients as cadaveric kidney donors

M. C. Foster,
P. W. Wenham,
P. A. Rowe*,
R. W. Blamey,
M. C. Bishop,
R. P. Burden* and
A. G. Morgan*

Departments of Surgery and
**Renal Medicine, Nottingham City*
Hospital, Hucknall Road,
Nottingham NG5 1PB, UK
Correspondence to:
Mr M. C. Foster

We have no fixed upper age limit for cadaveric kidney donors and donors over the age of 50 provided kidneys for 22 per cent of our adult transplant recipients between 1983 and 1986. Immediate function following transplantation occurred in 17 per cent of these kidneys compared with 58 per cent for kidneys from donors under the age of 50. The 1-year actuarial graft survival rate for transplants from donors over 50 was 52 per cent, compared with 70 per cent for transplants from donors under 50 ($P<0{\cdot}05$). Thus kidneys from older donors make an important contribution to the total pool of organs available for transplantation, but their use leads to inferior results in comparison with kidneys from younger donors.

Keywords: Renal transplants, donor age

There is no general consensus as to the upper age limit for cadaveric kidney donors[1], but the ever-widening gap between the size of the recipient waiting list and the number of transplants performed means that many units are being forced to use kidneys from donors who are older than is perhaps ideal.

We do not adhere to any formal criteria when deciding on the suitability of locally referred potential cadaveric renal donors or when accepting kidneys offered from other transplant centres. Each case is assessed individually and, assuming that the donor has no evidence of previous renal impairment, kidneys are used if the donor produces reasonable quantities of urine after a fluid challenge and if the creatinine concentration is not markedly elevated. In particular we have no upper donor age limit. We have therefore examined our results to assess the effects of increased donor age.

Patients and methods

One hundred and thirty cadaveric transplants were performed in adults between January 1983 and December 1986. To facilitate comparison between transplants from younger and older donors, transplants were divided into two groups, those who received kidneys from donors <50 years (younger donors, 101 transplants) and those who received kidneys from donors $\geqslant 50$ years (older donors, 29 transplants).

Comparisons between the groups have been made using the χ^2 test, Fisher's exact test, the Mann–Whitney *U* test and the Student's *t* test. Patients have been followed up for a minimum of 1 year. Actuarial graft survival rates have been calculated by the method of Peto *et al.*[2], and comparison between survival of the two groups was by the log rank test. All causes of graft failure including death with function have been included. All failed grafts were examined histologically. 'Technical failures' were those associated with absent renal perfusion due to vascular thrombosis. Graft function was defined as renal function obviating the need for dialysis: the onset of function therefore was taken to be the day after the last dialysis.

Donors

Donor age ranged from 11 to 76 years; the age distribution is shown in *Table 1*. All donors were ventilated and all passed >1200 ml of urine in the 24 h preceding removal of the kidneys and at least 50 ml in the final hour. All but one kidney (from a younger donor) were retrieved from heart-beating donors and all kidneys were stored in ice. Other donor related variables are shown in *Table 2*. Head injury was a significantly more frequent cause of donor death in younger donors while intracranial haemorrhage was commoner in older donors ($\chi^2=4{\cdot}01$, $P<0{\cdot}05$). Younger donors tended to be ventilated for longer periods, although this did not reach statistical significance. Creatinine concentrations were available for 90 donors, in the remainder only the urea was recorded. The mean creatinine for younger donors was 100 μmol/l (s.d. = 33) and for older donors 109 μmol/l (s.d. = 33). The number of donors with renal insufficiency (defined as creatinine >120 μmol/l or urea $>8{\cdot}0$ mmol/l) is shown in *Table 2*. Hypertension (defined as either a diastolic blood pressure of $\geqslant 100$ mmHg recorded during the terminal admission or as blood pressure which had previously required treatment) was more prevalent in older than in younger donors ($P<0{\cdot}001$, Fisher's exact test). Significantly more older donors had prolonged episodes of hypotension (systolic blood pressure of <90 mmHg for >2 h) before retrieval than younger donors ($\chi^2=4{\cdot}91$, $P<0{\cdot}05$). A similar number of older and younger donors received inotropic support. Ischaemic times were similar in each group.

Recipients

Recipients were selected on the basis of blood group compatibility, a negative cytotoxic cross-match and HLA-DR typing. All received at least one blood transfusion before transplantation. Immunosuppression was with prednisolone and azathioprine in 99 cases and prednisolone and cyclosporin in 31 cases. There was no difference between the groups in the immunosuppression used or in any other recipient-related risk factor. Details are shown in *Table 3*.

Results

Immediate graft function after transplantation occurred in 59 transplants (58 per cent) from donors <50 years but in only 5 (17 per cent) of those from donors $\geqslant 50$ years ($\chi^2=15{\cdot}3$, $P<0{\cdot}001$). The mean delay before function occurred (excluding those grafts which never functioned) was similar in the two groups (younger donor group 11 days, s.d. = 7; older donor group 13 days, s.d. = 8).

The causes of graft failure are shown in *Table 4*. Overall there were more graft losses in the older group ($\chi^2=4{\cdot}19$, $P<0{\cdot}05$) but the differences did not reach statistical significance for individual causes of graft failure.

The actuarial graft survival rates for transplants from donors aged <50 years and those from donors $\geqslant 50$ years are shown in *Figure 1*. The 1 and 3 year graft survival rates for kidneys from younger donors were 70 per cent and 58 per cent, those for kidneys from older donors were 52 per cent and 36 per cent ($\chi^2=4{\cdot}42$, $P<0{\cdot}05$).

The mean creatinine concentration 6 months after transplantation in patients with graft function whose kidneys came from younger donors was 147 μmol/l (s.d. = 58), which

Table 1 *Distribution of transplants according to age of donor*

Donor age (years)	10–19	20–29	30–39	40–49	50–59	60+
Number of transplants	27	33	23	18	19	10
Percentage of total	21	25	17	14	15	8

The data in this paper formed the basis of a presentation to the British Transplantation Society in Belfast in April 1987

0007–1323/88/080767–03$3.00

Table 2 *Donor-related variables*

	Donors <50 years ($n=101$)	Donors $\geqslant 50$ years ($n=29$)
Cause of death		
Head injury (%)	49 (49)	8 (28)
Intracerebral haemorrhage (%)	38 (38)	18 (62)
Other (%)	14 (14)	3 (10)
Median days on ventilator (range)	2·2 (1–12)	1·7 (1–5)
Number with renal insufficiency‡ (%)	16 (16)	6 (21)
Number with hypertension* (%)	3 (3)	8 (28)
Number with prolonged hypotension† (%)	24 (24)	13 (45)
Number requiring inotropic support (%)	33 (33)	12 (41)
Mean warm ischaemic time (min ± s.d.)	6·5 ± 3·8	6·0 ± 5·1
Mean total ischaemic time (h ± s.d.)	18·6 ± 6·9	16·4 ± 7·4
Mean anastomosis time (min ± s.d.)	45 ± 14	46 ± 15

* Defined as diastolic blood pressure $\geqslant 100$ mmHg recorded during terminal admission or as blood pressure which had previously required treatment; † defined as systolic blood pressure <90 mmHg for >2 h; ‡ defined as creatinine >120 μmol/l or urea >8 mmol/l

Table 3 *Recipient-related variables*

	Donors <50 years ($n=101$)	Donors $\geqslant 50$ years ($n=29$)
Mean recipient age (years ± s.d.)	35 ± 11	35 ± 12
Number of re-transplants	22 (22)	4 (14)
Number of sensitized patients	26 (26)	6 (21)
Mean HLA mismatches (± s.d.)	3·1 ± 1·5	3·1 ± 1·6
Number on cyclosporin as initial immunosuppression	26 (26)	5 (17)

Values in parentheses are percentages

Table 4 *Causes of graft failure*

	Donor <50 years ($n=101$)	Donor $\geqslant 50$ years ($n=29$)
Technical	4 (4)	4 (14)
Acute rejection	20 (20)	9 (31)
Chronic rejection	12 (12)	4 (14)
Death with function	4 (4)	1 (3)
Other*	1 (1)	
Total failures	41 (41)	18 (62)

Values in parentheses are percentages. * One graft from a donor <50 years failed after 3 months because of pyonephrosis

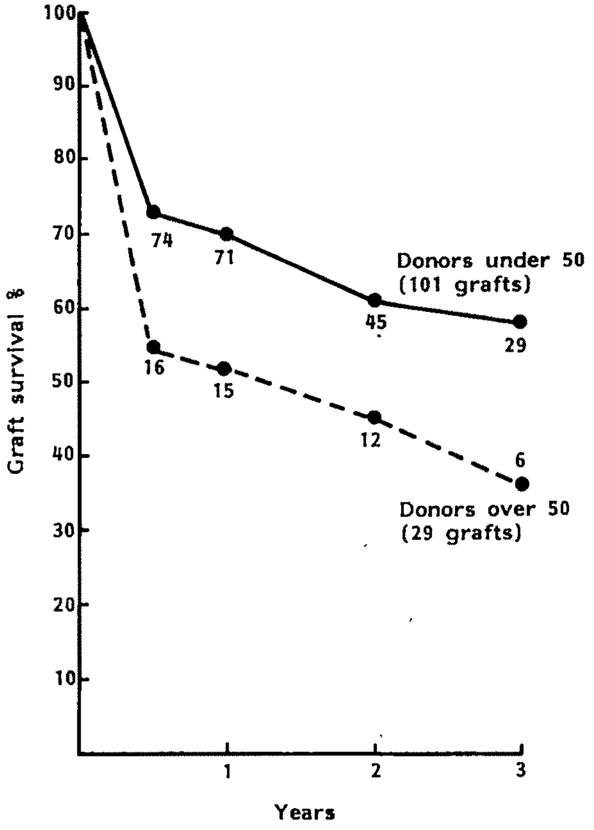


Figure 1 *Actuarial graft survival of transplants from donors $\geqslant 50$ years and from donors <50 years. The figures by each point indicate the number of grafts at risk at that time*

was not significantly different to that for kidneys from older donors (173 μmol/l, s.d. = 68).

Discussion

Our criteria for selection of donors are not as stringent as those recommended by some authors[3], and result in more kidneys being available for transplantation. Donors $\geqslant 50$ years provided kidneys for 22 per cent of the grafts in our series, compared with <2 per cent in a series of over 6000 American transplants[4], 4 per cent in over 8000 transplants reported to Eurotransplant[5], and 7 per cent in a single centre study in England[6]. Previous studies which have reported no detrimental effect of increased donor age[7–10] have contained 7 per cent of donors >45[7], 4 per cent >55[8] and 7 per cent >50[9] (in one analysis[10] the proportion of older donors is not given). Our data are in agreement with series in which inferior results are obtained using kidneys from older donors[4–6,11–13].

In four kidneys from older donors, radioisotope perfusion scans carried out in the first 48 h demonstrated no perfusion and exploration of the graft revealed vascular thrombosis and a non-viable graft (technical failure). Technical problems also occurred in kidneys from younger donors but the incidence was lower. Technical problems are most likely to occur following anastomoses involving diseased vessels which are more prevalent in older donors and are reflected in the higher prevalence of pre-morbid hypertension in these donors.

After exclusion of the technical failures only five of the remaining twenty-five kidneys from older donors had immediate function (20 per cent), compared with fifty-nine out of ninety-seven (61 per cent) kidneys from younger donors. Delayed function was due to acute tubular necrosis (ATN). Donor hypertension[14], terminal oliguria[4], the use of inotropic support[16], prolonged ischaemic times[9] and anastomosis time[16], previous transplants[9] and the presence of lymphocytotoxic antibodies in the recipient[17] have all been cited as factors associated with ATN; but with the exception of hypotensive episodes, which were more frequent in our older donors, these factors were similar in each group. As less than half our elderly donors had prolonged hypotension this alone cannot explain why 80 per cent of these kidneys developed ATN, and it may simply be that the ageing kidney is more susceptible.

There is conflicting evidence about the importance of ATN in determining the long-term outcome after transplantation[9,18], but postoperative management is more difficult if the kidney is not functioning, particularly if cyclosporin is used[19]. If it is used it is important to avoid high levels of cyclosporin in the blood, and consideration should be given to substituting it with alternative immunosuppressive agents after 2 weeks, if there is no function, to allow the kidney to recover from the nephrotoxic effects. Frequent biopsy of the kidney is necessary to exclude rejection. One-quarter of our kidneys with ATN from older donors and 18 per cent with ATN from younger donors never functioned at all. Serial biopsies performed on these patients demonstrated progressive rejection changes which caused graft failure before the ATN had time to recover In the remaining kidneys with ATN the mean time to the onset of function was similar in kidneys from younger and older donors.

The medium-term outcome for kidneys from older donors which survive the initial postoperative period is comparable to that of kidneys from younger donors. The incidence of graft loss from chronic rejection was similar in the two groups and there was no significant difference in creatinine concentration 6 months after successful transplantation.

Donors over 50 years make a significant contribution to the total number of organs available for transplantation In view of the chronic shortage of cadaveric kidneys we do not feel we are in a position to stop using them. The results obtained from these kidneys are inferior to those obtained with kidneys from younger donors, with more grafts being lost due to technical failure and to acute rejection. Because of the susceptibility of kidneys from older donors to ATN, efforts should be made to minimize other risk factors. Many of these cannot be altered in practice, but cold ischaemia can be reduced if the kidneys are used as soon as possible and unsensitized patients having first grafts should be selected to be recipients.

References

1. Taylor RMR, Ting A, Briggs JD. Renal transplantation in the United Kingdom and Ireland—the centre effect. *Lancet* 1985, **i**: 798–802.
2. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II Analysis and examples *Br J Cancer* 1977; **35**. 1–39.
3. Evans DB, Raftery A Kidney transplantation In Calne RY, ed *Transplantation Immunology—Clinical and Experimental* Oxford Oxford University Press, 1984: 413–36.
4. Lucas BA, Vaughn WK, Spees EK, Sanfilippo F Identification of donor factors predisposing to high discard rates of cadaver kidneys and increased graft loss within one year post transplantation—SEOPF 1977–82. *Transplantation* 1987, **43** 253–8.
5. Pleog RJ, Visser MJT, Stijnen T, Persijn GG, van Schilfgaarde R Impact of donor age and quality of donor kidneys on graft survival *Transplant Proc* 1987; **19**. 1532–4
6. Geoghegan T, Digard N, Leppington L, Harris KR, Slapak M Functional and other parameters in assessment of cadaveric kidneys for transplantation *Transplant Proc* 1984; **16** 64–6
7. Van Speybroeck J, Feduska N, Amend W, Vincenti F, Cochrum K, Salvatierra O Influence of donor age on graft survival *Am J Surg* 1979; **137**: 374–6.
8. O'Connor KJ, Franklin C, Bradley JW, Cho SI The effect of increased donor age on kidney transplant outcome. *Transplant Proc* 1986, **18** 480–1.
9. Kahan BD, Mickey R, Flechner SM *et al* Multivariate analysis of risk factors impacting on immediate and eventual cadaver allograft survival in cyclosporin-treated recipients *Transplantation* 1987; **43**: 65–70
10. Tiwari J, Teraski PI, Mickey MR Factors influencing kidney graft survival in the cyclosporin era: a multivariate analysis *Transplant Proc* 1987, **19**. 1839–41
11. Darmandy EM Transplantation and the aging kidney. *Lancet* 1974; **ii** 1046–7.
12. Sinclair NR, Jeffrey JR, Keown PA, Stiller CR Risk factors and HLA matching in renal transplantation using cyclosporine therapy *Transplant Proc* 1986: **18** 1234–5.
13. Hong JH, Shirani K, Arshad A *et al.* Influence of cadaver donor age on the success of kidney transplants *Transplantation* 1981, **32**: 532–4
14. Canadian Multicentre Transplant Study Group A randomized clinical trial of cyclosporine in cadaveric renal transplantation *N Engl J Med* 1983, **309** 809–13
15. Schneider A, Toledo-Pereyra LH, Zeichner WD, Allaben R, Whitten J Effect of dopamine and pitressin on kidneys procured and harvested for transplantation *Transplantation* 1983; **36** 110–11.
16. Ontario Renal Transplant Research Group Factors contributing to primary non function of cadaver kidney transplants *Transplant Proc* 1986, **18**: 516–18
17. Iwaki Y, Iguro T, Terasaki PI. Nonfunctional kidneys in immunized patients *Transplant Proc* 1985, **17**: 2449–51
18. Canafax DM, Torres A, Fryd DS *et al* Effects of delayed function on recipients of cadaver renal allografts *Transplantation* 1986, **41** 177–80
19. Salaman JR Cyclosporin in renal transplantation A guide to management. *Lancet* 1984; **ii**: 269–71

Paper accepted 29 March 1988

Br. J. Surg. 1988, Vol. 75, August,
770–773

DNA ploidy pattern and tumour spread in gastric cancer

X. de Aretxabala,
Y. Yonemura,
K. Sugiyama, T. Kamata,
K. Konishi, K. Miwa and
I. Miyazaki

Department of Surgery II, School of Medicine, Kanazawa University, Kanazawa, Ishikawa 920, Japan

Correspondence to:
Dr X de Aretxabala,
Department of Surgery, Faculty of Medicine, Universidad de la Frontera, P O Box 54-D, Temuco, Chile

The DNA ploidy pattern of gastric cancer was studied in 58 patients to investigate the heterogeneity between primary tumour and metastases. In both primary tumours and lymph node metastases, diploid patterns accounted for 33 per cent, whereas all liver metastases were aneuploid. The percentage of polyploid cells was higher in the liver metastases than in primary tumours and lymph node metastases. When the heterogeneity of DNA ploidy pattern between primary tumour and metastasis was evaluated, diploid tumours had a significantly lower rate of lymph node metastasis heterogeneity than aneuploid tumours. When the DNA ploidy pattern and survival were evaluated, the patients who had a diploid pattern in both primary tumour and metastasis had a significantly higher survival rate than the patients who had an aneuploid pattern in the primary tumour and metastasis (57 per cent versus *26 per cent at 5 years). These data suggest that cell heterogeneity is a common phenomenon in gastric cancer, and this may be important in the evolution of the disease. Furthermore, the role of the DNA ploidy pattern as a prognostic factor is emphasized.*

Keywords: Gastric cancer, DNA ploidy pattern, heterogeneity

In a variety of malignant tumours there is increasing evidence of a relationship between the DNA ploidy pattern and prognosis. In these reports, the presence of an aneuploid type of pattern has been associated with a worse prognosis[1–7]. Studies have shown the capacity of malignant cells to differ with respect to many phenotypes, including immunogenicity, growth rates, cell surface receptor, susceptibility to cytotoxic drugs and propensity for invasion and metastasis[7–15]. By studying the nuclear content of DNA, different types of pattern can be detected and the changes occurring in the composition of tumours during the evolution of the cancer can be analysed.

To obtain further information on the DNA ploidy pattern during the time the cancer was spreading, we studied the DNA ploidy pattern in primary tumours and metastases in individual patients and evaluated the relationship between the heterogeneity of the DNA ploidy pattern and the clinical prognosis.

Patients and methods

Fifty-eight patients with gastric cancer who were admitted to the Department of Surgery II of Kanazawa University were studied. Only patients with histological specimens from the gastric cancer and metastasis suitable for DNA analysis and histological evaluation were included. Follow-up ranged from several months to 12 years.

For the DNA measurement, a paraffin-embedded sample of tissue measuring 2 × 2 × 2 mm and containing cancer cells was taken from the portion just adjacent to the haematoxylin and eosin stained section. After dewaxing, the specimen was hydrated in decreasing concentrations of ethanol, then incubated twice during a 1-h period: first, in a Hank's solution containing 0·2 per cent Na-EDTA (Dojin, Japan) at 60°C and, secondly, at 37°C in a Hank's solution containing 0·02 per cent collagenase type IV (Cooper Byo Medical) and albumin 0·2 per cent (Wako Pure Chemical Industries Ltd, Japan). At the end of this procedure, the sample tissue was homogenized and the homogenates were filtered through a nylon mesh (50 μm). The specimen was then incubated in a Hank's solution containing 0·2 per cent Na-EDTA for 12 h at 60°C. Following this, the cells were incubated for 30 min in a Hank's solution containing 0·1 per cent RNAse (Sigma Chemical Co., St Louis, Missouri, USA) and stained with 0·0025 per cent propidium iodide (Sigma Chemical Co., St Louis, Missouri, USA) in sodium citrate.

The DNA was measured by means of a cytophotometer (Olympus BH2-QRFL, Tokyo, Japan). Gastric cancer evaluation was done according to the Japanese Research Society for the Gastric Cancer Study[16]. About 100 cancer cells and 20 stromal lymphocytes were measured in each specimen; the average of the 20 lymphocytes was considered the 2c value. The DNA peak was considered diploid when it deviated less than 20 per cent from the diploid standard. One peak was considered independent from another when it contained at least 50 per cent of the number of cells contained in the other peak, and when it deviated from another peak by at least 0·2c.

Patients were arbitrarily divided into two groups according to the percentage of polyploid cells: group A patients had ≥10 per cent of cancer cells with an amount of DNA greater than 6c and group B patients had <10 per cent of cancer cells with an amount of DNA greater than 6c. The different types of histograms were divided into four groups according to the classification proposed by Hatton *et al.* (*Figure 1*)[17].

Tabular data were studied using a χ^2 test. Actuarial survival figures were calculated using the Kaplan–Meier method[18]. The generalized Wilcoxon test was employed in the analysis of survival rates. Causes of death due to operative complications and causes other than the tumour were excluded from the study. An observation was considered to be statistically significant if $P<0·05$.

Results

Among the primary tumours, a diploid DNA pattern was observed in 19 patients (33 per cent). In the 39 patients who had an aneuploid pattern, type B accounted for 18 patients (31 per cent), type C for 19 (33 per cent) and type D for 2 patients (3 per cent). In the 54 patients in whom lymph node metastases were studied, a diploid pattern was seen in 18 patients (33 per cent), type B in 22 (41 per cent), type C in 13 (24 per cent) and type D in one patient. In the 11 patients in whom liver metastases were studied, type B was observed in 7 patients (64 per cent) while types D and C were seen in 3 patients (27 per cent) and 1 patient respectively. The DNA ploidy pattern of metastases was evaluated in relation to the pattern of primary tumours. In the 17 patients with a diploid pattern in the primary tumour in whom lymph node metastases were studied, lymph node metastases were diploid in 12 (71 per cent) and aneuploid in 5 (29 per cent) patients respectively. On the other hand, among the 37 patients with an aneuploid pattern in the primary tumour in whom lymph node metastases were studied, a diploid pattern in the lymph node metastasis was observed in 6 patients (16 per cent).

In the 16 patients who had a type B pattern in the primary tumour, 11 had the same type of pattern in the lymph node metastasis, yet in 3 the main peak was in a different position in

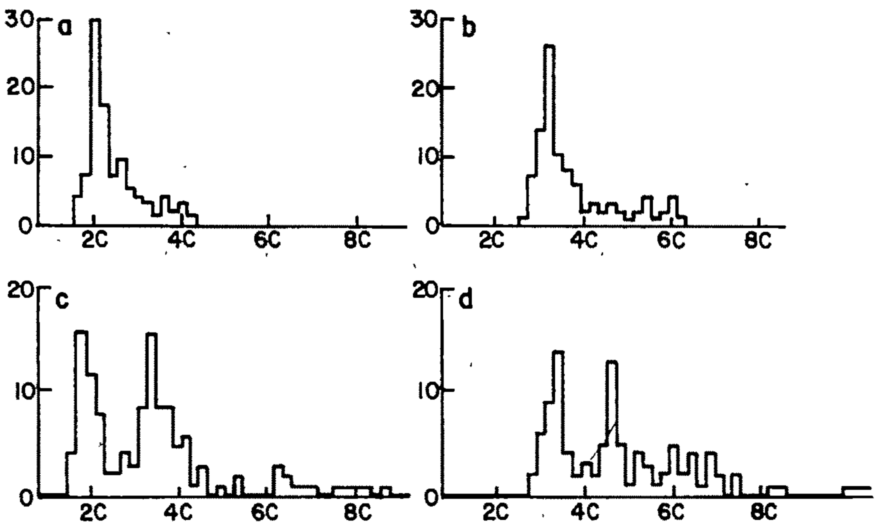


Figure 1 *Ploidy patterns of gastric carcinomas.* **a** *Type A diploid carcinoma,* **b** *type B heteroploid carcinoma with polyploid population,* **c** *type C mosaic of diploid and heteroploid stem lines with polyploid populations,* **d** *type D mosaic of heteroploid stem lines with polyploid population*

Table 1 *Types of pattern in primary tumours and their lymph node metastases*

Primary tumour (*n*)	Lymph node metastasis	No. of patients with the same type of pattern yet different DNA content
A (17)	A=12 (70·6%)	
	B=—	
	C= 5 (29·4%)	
	D=—	
B (16)	A= 1 (6·3%)	
	B=11 (68·7%)	3
	C= 4 (25%)	
	D=—	
C (19)	A= 5 (26·3%)	
	B=10 (52·6%)	
	C= 4 (21·1%)	1
	D=—	
D (2)	A=—	
	B= 1 (50·0%)	
	C=—	
	D= 1 (50·0%)	

$P<0{\cdot}01$ between the heterogeneity of lymph node metastases of diploid and aneuploid tumours

comparison with the primary tumour (*Table 1*). Among the 19 patients who had a type C pattern in the primary tumour, aneuploid lymph node metastases were type B in 10 patients and type C in 4. Finally, in the two patients who had a type D pattern in the primary tumour, lymph node metastases were type D in one patient and type B in the other.

In the three patients who had liver metastases and a type A pattern in the primary tumour, the DNA ploidy patterns of the liver metastases were type B in two and type D in one patient. In the five patients with liver metastases and a type B pattern in the primary tumour, liver metastases were type B in four patients and type D in one patient. Finally, in the three patients who had a type C pattern in the primary tumour, the DNA ploidy patterns of the liver metastases were type B, C, and D respectively.

The rate of lymph node metastasis heterogeneity was significantly higher in patients with aneuploid pattern in the primary tumour than in those with a diploid pattern (*Table 1*).

The DNA ploidy pattern of three primary tumours and their respective lymph node metastases are shown in *Figure 2*.

When the patients were studied in relation to the percentage of polyploid cells, 23 patients (40 per cent) had ≥10 per cent of over 6c cells in the primary tumours while 17 (32 per cent) of the 54 patients with lymph node metastases had ≥10 per cent of over 6c cells in the metastases. Conversely, 5 (45 per cent) of the 11 patients with liver metastases had ≥10 per cent of over 6c cells (*Table 2*).

The ploidy pattern of primary tumours and metastases was compared with other prognostic factors such as level of lymph node involvement, clinical stage and depth of wall invasion For this purpose, patients were divided into four groups according to the DNA ploidy pattern of the primary tumour and lymph node metastasis. Overall, those patients with an aneuploid pattern in either lymph node metastasis or primary tumour were more commonly observed to have more advanced disease. However, only the group of patients who had an aneuploid pattern in the lymph node metastasis and a diploid pattern in the primary tumour had a statistically significant association with more advanced lymph node involvement ($P<0.05$, *Table 3*).

Fifty-two patients who had lymph node DNA pattern analysis and a complete follow-up were studied. The patients were divided according to the type of ploidy pattern of lymph node metastasis and primary tumour. Those with a diploid pattern in both primary tumour and lymph node metastasis had a higher survival rate than patients in whom primary tumour and lymph node metastasis were aneuploid (57 per cent versus 26 per cent at 5 years, $P<0{\cdot}05$) (*Figure 3*).

Because the number of patients who had an aneuploid primary tumour and a diploid pattern in the lymph node metastasis (and vice versa) was small, these groups were excluded from the survival analysis.

Finally, the effect of heterogeneity on survival was studied in patients who had an aneuploid pattern in both primary tumour and metastasis. The survival of patients with the same aneuploid peak in both lymph node metastasis and primary tumour did not differ significantly from those who had different aneuploid peaks (*Figure 4*).

Discussion

The DNA content of primary tumours and their respective metastases were analysed by studying isolated nuclei of gastric cancer cells. To diminish the possibility of sampling error, only fragments of tumours containing more than 80 per cent of cancer cells were taken. Because of this prerequisite, lymph nodes with small areas of cancer involvement could not be

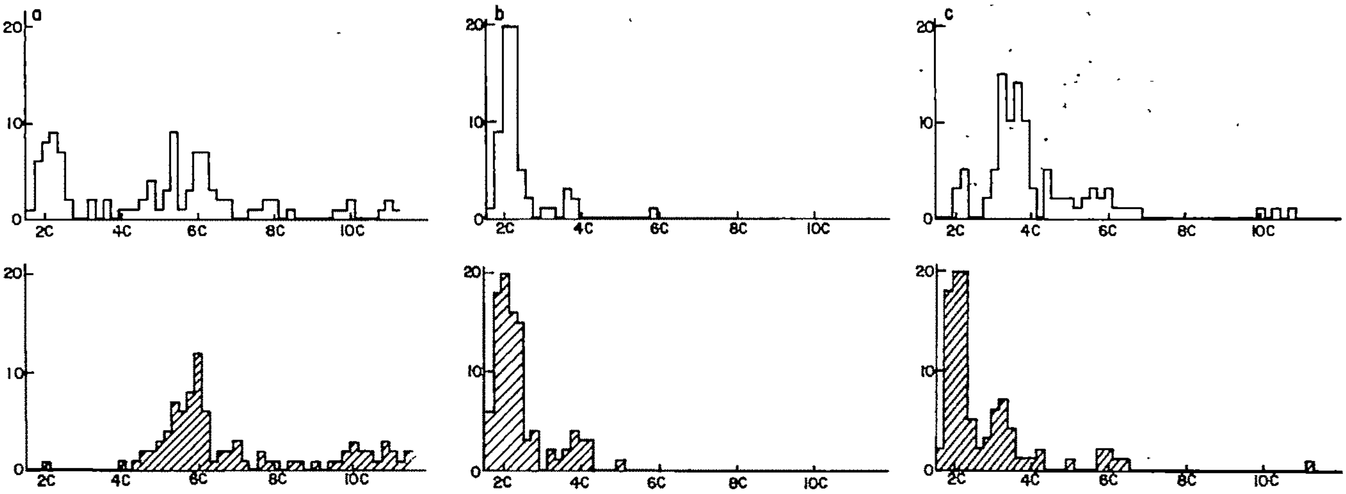


Figure 2 *DNA histograms obtained in primary tumours* □ *and lymph node metastases* ▨. **a** *Aneuploid primary tumour (type C) and aneuploid lymph node metastasis (type B),* **b** *diploid DNA content in both primary tumour and lymph node metastasis (type A),* **c** *aneuploid primary tumour (type B) and diploid lymph node metastasis (type A)*

Table 2 *Percentage of polyploid cells in primary tumours and metastases*

	≥10% of over 6c cells	<10% of over 6c cells
Stomach (primary tumour)	23 (39·7%)	35 (60·3%)
Lymph node metastases	17 (31·5%)	37 (68·5%)
Liver metastases	5 (45·5%)	6 (54·5%)

examined. The proportion of the different types of DNA pattern among the primary tumours was similar to that of previous reports[17,19]. However, in our group of patients the proportion of aneuploid tumours was slightly higher, possibly because the study was limited to tumours with secondary spread in the lymph node and liver. As reported previously, the aneuploid DNA pattern was associated with a worse prognosis. In the lymph node metastases, the distribution of the different types of patterns was very similar to that in the primary tumours. On the other hand, among the liver metastases only aneuploid types of tumours were observed. This may be explained by the more aggressive behaviour that has been reported for aneuploid tumours.

The study of the DNA ploidy pattern of metastases in relation to the primary tumour revealed the presence of DNA ploidy pattern heterogeneity. This divergence between primary tumours and metastases may be explained by the presence of changes in the ploidy pattern along with the cancer progression. This may determine the expression of different types of clones in the metastasis compared with that in the primary tumour. Reports from experimental studies have shown that metastatic cells have a higher rate of spontaneous mutation than non-metastatic cells, suggesting that metastatic cells may become heterogeneous[11,20]. In the genesis of this phenomenon, not only factors associated with the tumour are implicated, but also host factors could act by selecting tumoral subpopulations within the tumour[15,20,21]

On the other hand, clones that pre-existed within the primary tumour, yet were not observed in the analysed sample, may in part explain the differences between primary tumour and metastasis[8,14,15]. This clonal diversity has clinical importance because it means not only that metastasis and primary tumour may differ in their clinical behaviour, but also that individual cells within a tumour may differ from one another. Diploid types of tumours had a significantly lower rate of heterogeneity than aneuploid tumours. This higher stability may be associated with the better clinical prognosis that has been reported for diploid tumours.

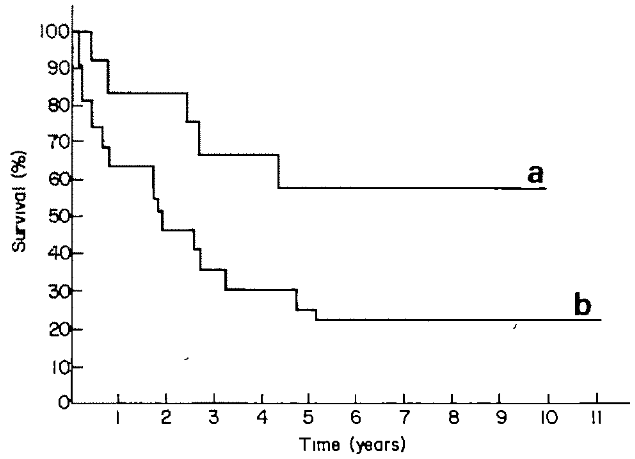


Figure 3 *Overall survival in patients with homo-heterogeneous DNA ploidy pattern (Kaplan–Meier).* **a** *Patients (n = 12) with a diploid pattern in both primary tumour and lymph node metastasis,* **b** *patients (n = 30) with an aneuploid pattern in both primary tumour and lymph node metastasis. P<0·05*

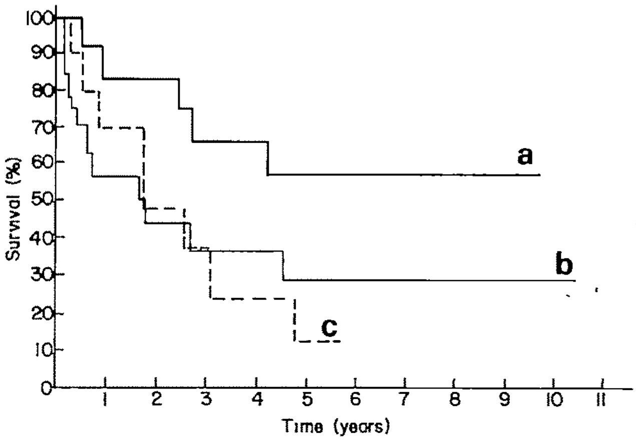


Figure 4 *Overall survival in patients with homo-heterogeneous DNA ploidy pattern (Kaplan–Meier).* **a** *Patients (n = 12) with diploid pattern in both primary tumour and lymph node metastasis,* **b** *patients (n = 19) with the same aneuploid pattern in both primary tumour and metastasis;* **c** *patients (n = 11) with a different aneuploid pattern in primary tumour and lymph node metastasis*

Table 3 *Distribution of ploidy of primary tumours and lymph node metastases according to extension of lymphatic spread, clinical stage and depth of wall invasion*

Primary tumour	Lymph node metastasis	Node involvement		Stage			Wall invasion			
		(n1+n2)	(n3+n4)	II	III	IV	sm+pm	ss	sei	*n*
Diploid	Diploid	83	17*	50	33	17	33	50	17	12
Aneuploid	Aneuploid	71	29	42	16	42	32	35	32	31
Diploid	Aneuploid	—	100*	—	—	100	—	40	60	5
Aneuploid	Diploid	67	33	17	33	50	33	33	33	6

Numbers in table are percentages of patients

sei, Spread to serosa and/or infiltration of other organs; ss, spread to subserosa; pm, spread to muscularis propria; sm, spread to submucosa; *n*, number of patients

* $P < 0.05$

In a previous study[22] a relationship was observed between the percentage of polyploid cells and survival in early gastric cancer. In the majority of cases, this cell population represents the growth population of an aneuploid stem line. However, the presence of a peak at that level may also represent the existence of a $> 6c$ stem line. We decided arbitrarily to divide the patients in our study into two groups according to the percentage of polyploid cells. When the relationship between the percentage of polyploid cells and the compromised organ was studied, although the differences did not reach statistical significance, the percentage of polyploid cells in the liver metastasis was higher than that in stomach and lymph nodes. This tendency may be explained by the higher malignancy of aneuploid cells.

The number of patients who had an aneuploid lymph node metastasis and a diploid primary tumour and vice versa was small, and thus we were unable to study these groups in relation to survival. On the other hand, when patients who had a diploid pattern in both lymph node metastasis and primary tumour were compared with those in whom lymph node metastasis and primary tumour were aneuploid, we could confirm the worse prognosis which has been associated with an aneuploid pattern.

Finally, no differences in survival were observed in the patients who had an aneuploid pattern in both lymph node metastasis and primary tumour, irrespective of whether they had the same or a different aneuploid peak. However, these groups of patients were small and no definitive conclusions can be drawn. From the current findings, it can be concluded that tumour heterogeneity is a phenomenon which is present in the evolution of gastric cancer. This phenomenon may be an important factor in the clinical evolution of cancer and deserves further study to identify its significance in the prognosis and management of cancer patients. The importance of the DNA ploidy pattern in the evaluation of patients with gastric cancer is emphasized.

References

1. Kokal WA, Duda RB, Azumi N *et al.* Tumor DNA content in primary and metastatic colorectal carcinoma. *Arch Surg* 1986; **121**: 1434–9
2. Hedley DW, Rugg CA, Ng ABP, Taylor IW. Influence of cellular DNA content on disease-free survival of stage II breast cancer patients. *Cancer Res* 1984; **44**: 5395–8.
3. Korenaga D, Okamura T, Sugimachi K, Inokuchi K. Prognostic study of intramucosal carcinoma of the stomach with DNA aneuploidy. *Jpn J Surg* 1985; **15**: 443–8.
4. Frankfurt OS, Chin JL, Englander LS, Greco WR, Pontes JE, Rustum YM. Relationship between DNA ploidy, glandular differentiation, and tumor spread in human prostate cancer. *Cancer Res* 1985; **45**: 1418–23.
5. Rodenburg CJ, Cornelisse CJ, Heintz PA, Hermans J, Jan Fleuren G. Tumor ploidy as a major prognostic factor in advanced ovarian cancer. *Cancer* 1987; **59**· 317–23.
6. Atkin NB, Kay R. Prognostic significance of modal DNA value and other factors in malignant tumours based in 1465 cases *Br J Cancer* 1979; **40**: 210–21.
7. Ljungberg B, Stenling R, Roos G. DNA content and prognosis in renal cell carcinoma. A comparison between primary tumors and metastases. *Cancer* 1986; **57**: 2346–50
8. Ljungberg B, Stenling R, Roos G. DNA content in renal cell carcinoma with reference to tumor heterogeneity. *Cancer* 1985, **56**: 503–8.
9. Heppner GH. Tumor heterogeneity. *Cancer Res* 1984, **44**· 2259–65.
10. Talmadge JE, Benedict K, Madsen J, Fidler IJ. Development of biological diversity and susceptibility to chemotherapy in murine cancer metastases. *Cancer Res* 1984, **44**. 33801–5.
11. Fidler IJ, Hart IR. Biological diversity in metastatic neoplasms: origins and implications. *Science* 1987; **17**: 998–1003.
12. Cikes M, Klein G. Quantitative studies of antigen expression in cultured murine lymphoma cells surface antigens in 'asynchronous' cultures. *J Natl Cancer Inst* 1972; **49**: 1599–1606
13. Wang N, Yu SH, Liener IE, Hebbel RP, Eaton JW, McKhann CF. Characterization of high and low metastatic clones derived from a methylcholanthrene induced murine fibrosarcoma. *Cancer Res* 1982; **42**: 1046–51.
14. Hidemann W, Roessner A, Wörmann B *et al.* Tumor heterogeneity in osteosarcoma as identified by flow-cytometery. *Cancer* 1987; **59**: 324–8.
15. Nelson KG, Haskill JS, Sloan S *et al.* Flow cytometric analysis of human uterine sarcomas and cell lines. *Cancer Res* 1987; **47**: 2814–20.
16. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. Part I. *Jpn J Surg* 1981; **11**: 127–39.
17. Hattori T, Hosokawa Y, Fukuda M, Sugihara H, Hamada S, Takamatsu T Analysis of DNA ploidy patterns of gastric carcinomas of Japanese. *Cancer* 1984; **54**: 1591–7.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**· 457–81.
19. Czerniak B, Fritz H, Koss L. DNA distribution patterns in early gastric carcinomas A Feulgen cytometric study of gastric brush smears. *Cancer* 1987; **59**: 113–7.
20. Cifone M, Fidler IJ. Increasing metastatic potential is associated with increasing genetic instability of clones isolated of murine neoplasms. *Proc Natl Acad Sci USA* 1981; **78**. 6949–52.
21. Ossowski L, Reich E Changes in malignant phenotype of a human carcinoma conditioned by growth environment. *Cell* 1983; **33**: 323–33.
22. de Aretxabala X, Yonemura Y, Sugiyama K, Kamata T, Konishi K, Miwa K, Miyazaki I DNA ploidy in early gastric cancer. *Br J Cancer* 1988 (in press).

Paper accepted 29 February 1988

Br. J. Surg. 1988, Vol. 75, August,
774–778

Reconstruction after excision of soft tissue sarcomas of the limbs and trunk

From a retrospective analysis of 180 surgical interventions for soft tissue sarcoma of the limbs and trunk, it was concluded that complete excision of the tumour can usually be achieved without sacrifice of major artery, vein, nerve or bone. In this series five major arteries were resected but only one required reconstruction. None of six resected major veins or seven resected nerves were reconstructed. Bone resection in the limb required plating in only two of eleven patients who had limb-sparing resection (there were nine amputations). Both in the limbs and the thorax, resection of bone often involved such a wide excision of the superficial soft tissues as to require a flap repair: four were used in the limbs and three in five chest wall resections. In the majority of operations (140/180) primary wound closure was possible. After 15 procedures for tumour predominantly involving the superficial tissues, split skin grafts were used. These were generally successful (13/15), even occasionally when high-dose radiotherapy had been given. In 16 cases earlier radiotherapy influenced the decision to use a flap repair. A total of 18 flap repairs were performed. In various situations Mersiline mesh (Ethicon, Ltd., UK), Silastic implants and omental swings were used. Wound breakdown in heavily irradiated tissues presented a major challenge for reconstruction. Although major reconstruction was required in only 27 operations (15 per cent), a thorough knowledge of the available methods of reconstruction and repair is essential to allow uninhibited resection with an optimal aesthetic and functional result.

Keywords: Soft tissue neoplasma, sarcoma, surgical flaps, wound healing

A. Stotter,
N. R. McLean*,
M. E. Fallowfield†,
N. M. Breach* and
G. Westbury*

*St. Mary's Hospital, London, *The Royal Marsden Hospital, London and †St. George's Hospital, London, UK*
Correspondence to:
Miss A. Stotter, Department of Surgery, St Mary's Hospital, Praed Street, London W2 1NY, UK

Surgery for soft tissue sarcoma (STS) should aim at wide excision where this is compatible with satisfactory function[1]. In the limbs most surgeons avoid amputation where possible. If the tumour is high grade, or a small resection margin has to be accepted to preserve function, adjuvant high-dose radiotherapy will be necessary to achieve local control[2–7]. However, patients with STSs may initially be referred to general or orthopaedic surgeons who may have little personal experience of this rare malignancy and who may deal with the lesion by limited excision with or without radiotherapy. Even after optimal treatment of the primary lesion, local recurrence is common. In the National Cancer Institute series, for instance, four out of 27 patients developed local recurrence of the tumour[7]. The surgeon with a special interest in STS is therefore often faced with recurrent tumour in an area already affected by previous surgery and irradiation. In the case of radiation-induced sarcomas[8] the radiation damage may be particularly marked.

STS may invade bone, but invasion of major arteries, veins or nerves is relatively uncommon[9]. When it occurs, the problems of reconstruction are inevitably greater.

We have retrospectively analysed 180 consecutive operations for STS of the limbs and trunk performed by one general surgeon (G.W.), with the support of a reconstructive surgeon (N.M.B.), over the period 1982–1986.

Patients and methods

Over the study period 227 patients with histologically proven STS were referred, 156 had surgery for a tumour in the limbs or trunk and 14 of these patients had two or more operations, giving a total of 180 procedures Eighty-seven (48 per cent) of the operations were for previously unresected primary tumour and 93 for a recurrence; 56 (31 per cent) of the operations followed treatment of the tumour-bearing area by radiotherapy at an earlier time; three tumours appeared to be radiation-induced. Eighty-four of the 124 operative fields that had not previously been irradiated received treatment near the time of the index operation (usually postoperatively but occasionally pre- or split pre- and postoperatively). Thus overall 140 operations (78 per cent) were performed in tissue fields previously irradiated or irradiated perioperatively

Treatment during the study period aimed at limb-sparing resection of the primary or locally recurrent tumour with a radical or wide margin where possible, together with radiotherapy if the sarcoma was high grade. In the limbs and limb girdles 68 per cent of the tumours arose either in areas not limited by fascial boundaries (femoral triangle, axilla, etc.) or traversing the nearest fascial boundary at the time of presentation[10] Compartmentectomy, which may be appropriate for a tumour placed centrally within a musculo-fascial compartment[4], could not therefore be used regularly (A. T. Stotter, E. M Fallowfield, G. Westbury, unpublished results). If the tumour lay near structures important for function a smaller resection margin was accepted and adjuvant radiotherapy used, provided maximal dosage had not previously been given. However, macroscopic tumour was always removed even if artery, vein, nerve or bone had to be sacrificed to achieve this.

All cases were histologically reviewed at the Royal Marsden Hospital and patients were fully staged, including a computed tomographic (CT) scan of the primary site if local tumour was evident or suspected and the lungs if the standard chest X-ray was clear We have previously reported the value of CT scanning before surgery for primary or recurrent tumour[10].

Results

The reconstructions used are summarized in *Table 1*.

Special structures

Artery. Frank invasion of major arteries was uncommon; the vessel could be separated easily by dissection in the subadventitial plane in 22 of 27 operations where tumour was

Table 1 *Reconstructions used following 180 excisions of soft tissue sarcoma*

No.	Reconstruction	Type	
1	Arterial bypass		
2	Bone plates		
17	Flaps	Skin	(5)
		Muscle + split skin graft (1 also used over a bone plate)	(2)
		Myocutaneous	(6)
		Free	(4)
7	Other	Mersilene mesh	(2)
		Breast implant	(2)
		Omental swing	(3)

These 27 represent 15 per cent of the 180 procedures performed

Table 2 *Tumour characteristics resulting in amputation in 9 of the 180 operations for soft tissue sarcoma*

No.	Amputation	Indication
1	Thumb	Soft tissue recurrence; good clearance not otherwise possible
1*	Above knee	Fourth local recurrence of leg sarcoma; now involving tibia
1*	Below knee	Second recurrence of foot tumour; previous surgery + radiotherapy; now involving bone
2*	Hindquarter	Recurrent tumour involving bones of hip joint
3	Hindquarter	Massive soft tissue recurrence including upper thigh/groin
1*	Above elbow	Forearm tumour recurrent after surgery and radiotherapy, involving ulna

* Bone infiltrated by tumour

close. In these 22 patients treated by vessel-sparing excision and subsequent radiotherapy, no local (juxta-arterial) recurrences were encountered.

Five major arteries were excised. Four were not reconstructed, namely the radial on one occasion and the profunda femoris on three occasions. In the fifth patient, tumour was excised *en bloc* with the superficial femoral artery and vein; the artery only was replaced using a reversed saphenous vein graft from the same side.

Vein. Excision of a segment of major vein seldom led to disabling symptoms. The external iliac vein was excised once and the femoral vein on five occasions without reconstruction. All these wounds were irradiated. Of the five legs in which the superficial femoral vein was excised, one suffered persistent mild oedema and one had moderate oedema complicated by an episode of cellulitis 10 months postoperatively while on chemotherapy. After the one excision of the external iliac vein the patient had persistent moderate oedema. The lack of serious sequelae from vein resection is a measure of the enormous venous reserve in the limbs.

Nerve. As in the case of arteries, tumour rarely invaded major nerves and dissection was usually possible in the subepineural plane. The sciatic nerve required resection in two patients, the femoral nerve in two and the accessory nerve, musculocutaneous nerve and nerve to latissimus dorsi were each excised once. Nerve-grafting may have a role in selected cases but was not used in this series because remarkably good limb function can be maintained after excision even of major nerves such as the sciatic[4].

Bone. Ninety per cent of the operations were for tumour in a limb or limb girdle. Nine patients had amputations. *Table 2* shows that amputation was generally necessary because of extensive soft tissue tumour recurrence after previous surgery and radiotherapy. In five cases there was direct invasion of bone in addition.

Eleven limb-sparing operations included bone resection (*Table 3*). Five specimens showed histological evidence of infiltration; in the other cases the cortical layer of a bone was removed to provide an extra margin of clearance. For dispensable bones such as the fibula, a full thickness segment could be sacrificed without functional loss.

Bone plating was required in two patients, in one following half thickness sagittal resection of the shaft of the humerus. In the second patient, a nearly circumferential tumour of the forearm, recurrent after repeated surgery and radiotherapy to the point of tissue necrosis, was resected together with a full thickness segment of the ulna. The soft tissue defect was repaired with a groin pedicle flap (*Figure 1*). Two years later the radius fractured and was plated; it healed despite the previous irradiation.

For five chest wall tumours, deficits following excision included one or more ribs and, in two cases, part of the sternum. In one patient no skeletal reconstruction was used; in one Mersilene mesh was used to replace the deep defect. Three flaps were used: a skin flap, a latissimus dorsi muscle flap covered with split skin, and a rectus abdominis flap. The latter two were used in patients with radiation-induced sarcoma involving the sternum, one 25 years after radical mastectomy and radiotherapy for breast cancer, the other six years after treatment for Hodgkin's disease.

Muscle. Limb function was surprisingly well retained even after loss of major muscle groups. While tendon transfer was considered, especially in the forearm, it was not done in any of the 12 patients with tumours at this site.

Muscle transposition was sometimes useful to provide cover for exposed bone or major neurovascular structures, and as a bed for split skin grafts. Sartorius was used routinely to protect the femoral vessels, and in one patient pronator teres was transposed across the radial artery in the forearm.

Wound closure

The majority of wounds (140/180) were closed by primary suture.

Fifteen wounds were covered with split skin grafts, with healing in all but two. Five of the 15 grafted wounds were in irradiated tissue and only one of these grafts failed to take (*Figure 2*). The single-skin grafted wound that was irradiated postoperatively also broke down. Meshed grafts were particularly valuable and used in difficult areas such as the back: one patient with a larger lumbar defect who had previously had

Table 3 *Limb-conserving surgery requiring excision of bone and used in 11 of the 180 operations*

Bone resected	Reconstruction
Most of scapula*	None
Partial thickness of humerus*	Plate covered by transposed muscle and split skin graft
Medial epicondyle	Flap repair
75 per cent of ulna (3 previous tumour resections and 2 courses radiotherapy)*	Flap repair; fractured radius healed after plating
Part of ulna	None
Ilium	None
Femoral cortex	None
Posterior surface of femur	None
Segment of fibula	None
Part of calcaneum*	Flap repair
Part of calcaneum*	Flap repair

* Bone infiltrated by tumour

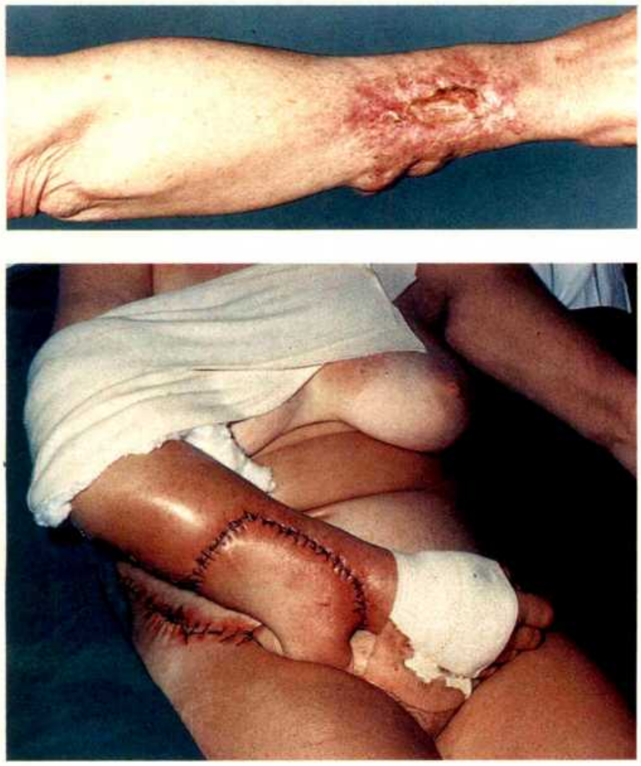


Figure 1 *Near circumferential tumour recurrence and radiation necrosis of the distal forearm. Three-quarters of the length of the ulna was excised with the specimen and the defect repaired with a pedicled groin flap*

40Gy radiotherapy to the area had a complete take of a meshed graft. In three patients in whom muscle was transposed from an area not irradiated, skin grafts also took successfully (*Table 4*).

Major soft tissue reconstruction was required on 25 occasions in 23 patients; one man had three successive flap repairs during the course of repeated surgery. Of these reconstructions, 18 comprised skin, muscle or myocutaneous flaps (*Table 4*). The circumstances in which flap repair was used were: defects following resection of tumours recurrent after both surgery and radiotherapy (13 operations); radiation-induced sarcomas (3 operations); extensive superficial soft tissue loss (14 operations), especially where bone was exposed; and major wound breakdown (3 operations).

Skin flaps were used on five occasions: two groin flaps, one dorsalis pedis flap, one skin transposition on the chest and a bipedicled flap to cover the patella. Muscle flaps covered with split skin (three cases) or myocutaneous flaps (six cases) were necessary to fill the more substantial defects. A superiorly based rectus abdominis flap, used for a chest wall defect, has already been referred to; an inferiorly based rectus abdominis flap was used after breakdown of a thigh wound. The use of the latissimus dorsi flap after excision of a radiation-induced sarcoma of the shoulder is illustrated in *Figure 2*. *Figure 3* shows a groin tumour, rapidly progressive during radiotherapy, which was excised and the wound closed with a tensor fasciae latae flap. The course of radiotherapy was completed through the flap.

Free flaps were used in four patients. Three latissimus dorsi free flaps were used (after excision of a tumour at the elbow, to repair a groin defect, and for persistent wound breakdown above the medial malleolus late after posterior compartmental resection of the calf muscles and radical dose irradiation). A free scapular flap was transferred to the foot. Two of the four free flaps failed. Although STS not uncommonly affects young patients who might be thought to be good candidates for free flap transfer, this may be comprised by radiation-induced vascular damage; older patients may have atheroma in the donor vessels.

Two patients (one already referred to above) had Mersilene mesh reconstruction to close defects, not involving overlying skin, on the chest wall and abdominal wall respectively. Two patients with primary sarcoma of the breast were treated by subcutaneous mastectomy with insertion of a subpectoral implant. Six operations in which no form of wound closure was used were all palliative cautery excisions of an extensive, circumferential dermatofibrosarcoma protuberans of the lower trunk.

Table 4 *Summary of flap reconstructions used in 18 cases after excision of soft tissue sarcomas*

No.	Type	Site
5	Skin	2 groin (1 pedicled) 1 dorsalis pedis 1 chest wall transposition 1 knee (bipedicled)
3	Muscle transposition + split skin graft	1 chest wall (latissimus dorsi) 1 forearm (pronator teres) 1 upper arm over a bone plate
6	Myocutaneous	2 tensor fasciae latae to groin 2 latissimus dorsi to shoulder 1 rectus abdominis to chest wall 1 rectus abdominis to thigh
4	Free microvascular	1 latissimus dorsi to elbow 1 latissimus dorsi to groin* 1 latissimus dorsi to calf 1 scapular to foot*

* Failed owing to anastomotic occlusion

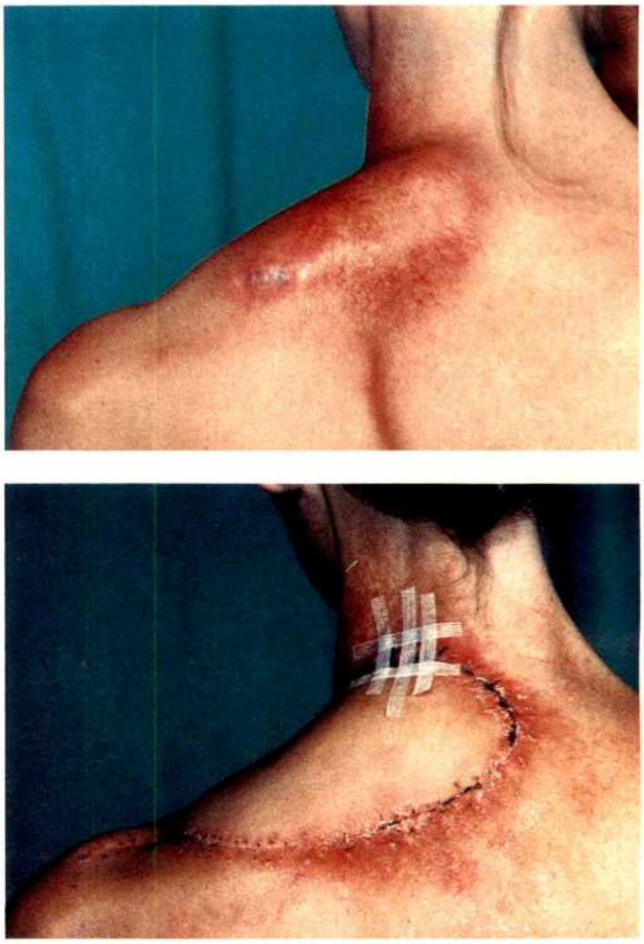


Figure 2 *A latissimus dorsi flap used for repair following removal of a radiation-induced sarcoma which presented 12 years after cure of the patient's Hodgkin's disease. She had received two courses of radiotherapy totalling 81 Gy to this area and the radiation damage can can be clearly seen*

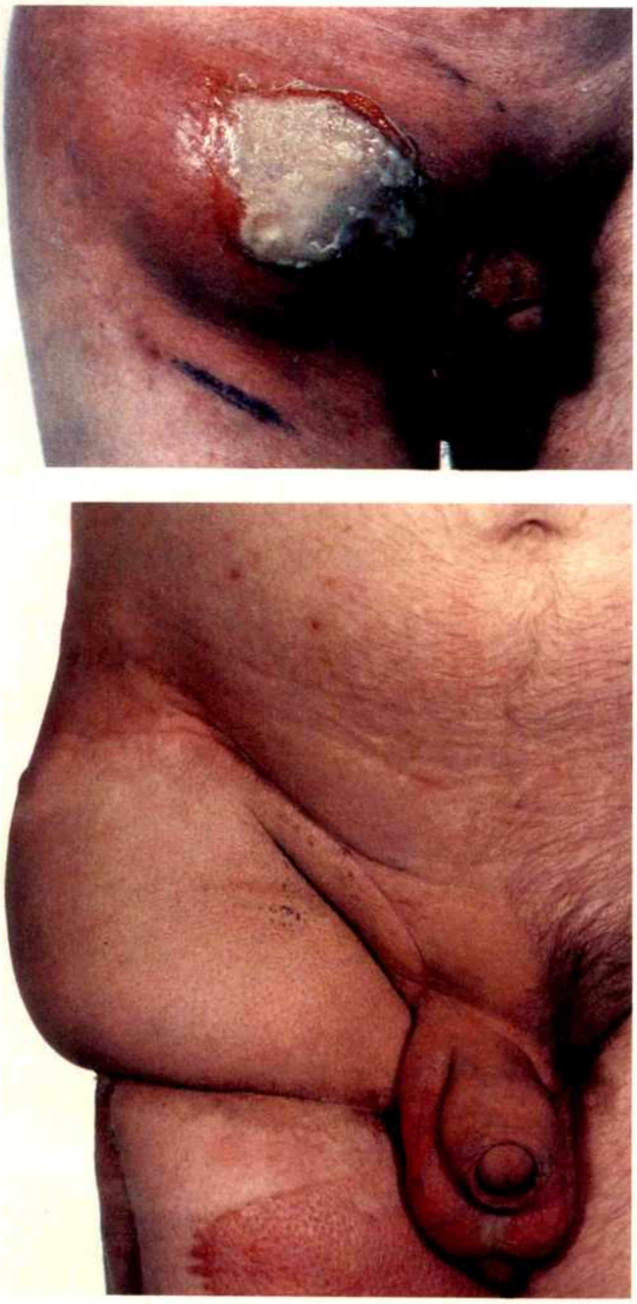


Figure 3 *Primary rhabdomyosarcoma of the groin progressive during radiotherapy. After excision the wound was closed with a tensor fasciae latae flap. The patient subsequently completed radiotherapy treatment, totalling 80 Gy, which did not prevent wound healing*

Wound breakdown

An important indication for soft tissue reconstruction is wound breakdown, especially following full dose irradiation (*Table 5*). Three flap repairs and three pedicled omental transpositions were used for this complication. The greater omentum was successfully employed as an aid to limb salvage in a patient who suffered delayed rupture of the superficial femoral artery in the base of a radio-necrotic wound 8 months following resection of a quadriceps tumour.

Table 5 *Antecedent treatment and management of six cases with major wound breakdown*

Site	Radiotherapy (Gy)	Previous closure	Repair
Thigh	66	Primary closure	Rectus abdominis flap
Groin	60	Free latissimus dorsi flap	Tensor fasciae latae flap
Calf	42	Primary closure	Free latissimus dorsi flap to residual unhealed wound 3 years later
Thigh	75·5	Primary closure	Omental swing (femoral artery bleed)
Groin	33 + 33 + 2	Primary closure	Omental swing (surgery for recurrence in hindquarter scar)
Thigh	39·6	Split skin	Omental swing

Discussion

The basis for wide or radical resection[1] for STS is the surgical pathology of the tumour. Invasion is initially limited by fascial boundaries but islands of tumour ('skip lesions') may be found at some distance from the main tumour mass, especially along intermuscular planes. While the grossly encapsulated appearance of most sarcomas invites surgical enucleation this, if used as the sole treatment modality, will almost inevitably lead to local recurrence because the surrounding pseudocapsule is lined by tumour cells.

Radiotherapy alone gives poor results[5,11] but improves local control when used as an adjunct to surgery particularly of high grade tumours and where surgical margins are narrow[1-6]. Regional[12] or systemic[3] chemotherapy may also improve control of the primary tumour. However, multimodality therapy inevitably increases the treatment-related morbidity[3,5,13]. In the short term, excluding haematological and cardiovascular complications of chemotherapy, the main problems are related to wound healing. In the long term oedema, fibrosis, stiffness and pain may limit function.

The proximity of structures important for function (arteries, nerves or bone) need not necessarily result in compromise of the resection margin provided reconstruction skills are available. Involvement of arteries by tumour was uncommon in this series as in others[3,9,14], but excision of the tumour with an adequate margin can still be performed when the tumour involves even a major artery since reconstruction using a reversed vein graft or a synthetic conduit is now widely practised[4,14,15].

Function after nerve excision is satisfactory in the lower limb without grafting[4]. This is not the case in the upper limb where the function of the hand is likely to be severely compromised. In this series, for tumours in the upper extremity, major nerves were preserved and marginal excision with adjuvant radiotherapy was used when possible. Nerve excision and grafting were not employed as the results are unpredictable[16].

Prosthetic replacement of bones and joints is a well established procedure for bone sarcoma but has limited application in the STSs[17]. Frank destruction of bone is usually associated with extensive soft tissue involvement and generally requires amputation[4]. On the other hand, when there is involvement of periosteum or minimal erosion of cortex, bone resection (partial or full thickness) may provide an adequate margin of tumour clearance[18]. The need for reconstruction may then be related to the extent of soft tissue loss rather than the skeletal deficit. Our one case in which delayed bone plating was required emphasizes the loss of bone strength after radiotherapy, which may be enhanced by the addition of cytotoxic therapy, especially intra-arterial chemotherapy[3,18].

In many sites, for example the hamstrings or the anterior or posterior compartment of the upper arm, excision of an entire muscle compartment is compatible with good limb function[4,19-21]. In the anterior thigh, total excision of quadriceps impairs knee stability and is therefore appreciably disabling. Where conservation of even one of the four heads with its nerve supply is compatible with a wide surgical clearance, acceptable knee function may be preserved[4]. In the forearm, muscle loss may cause a significant functional deficit in the hand and tendon transfer or joint stabilization may be considered though such procedures were not undertaken in this series.

Major reconstruction was required in only a minority (15 per cent) of these 180 operations (*Table 1*). In most cases the indication was the loss of a large volume of soft tissue, particularly if much skin and subcutaneous tissue were sacrificed and especially after previous radiotherapy. Where sites such as the groin and antero-medial thigh have been subjected to wide surgical clearance and high dose irradiation, repair using a well-vascularized flap protects major vessels, ensures primary healing and minimizes the risk of major secondary haemorrhage[22]. Over the period studied elective flap repair was used increasingly in such areas. Where bone has been removed with soft tissue, as in the thorax, a flap repair often provides a 'skeletal' reconstruction[23]. Both in the thorax and anterior abdominal wall, Mersilene mesh is an effective substitute for the deep layers[24].

It was necessary to draw on a wide range of reconstructive techniques, and each patient provided an unique problem that called for an individually tailored solution. As in other reported series, the use of flap closure, particularly in heavily irradiated areas, allowed uncomplicated wound healing[3,25]. The dominant factor in achieving local control is complete excision of the tumour[4,26]. In a proportion of cases, if amputation is to be avoided, complete excision is not possible without soft tissue reconstruction. The intelligent use of reconstructive techniques allows uninhibited limb-conserving excision with optimal aesthetic and functional results. Clearly a thorough knowledge of the available methods is essential for surgeons involved in the management of STS.

Acknowledgements

At the Royal Marsden Hospital our thanks are due to Mrs A. F. Mott, without whom a computer database of the sarcoma patients could not have been established. We also thank Dr C. Fisher for histological review and grading of the soft tissue sarcomas. Mr Harvey White performed the emergency omental transposition following femoral artery rupture. We are grateful to Mr M. N. Tempest, formerly Consultant Plastic Surgeon, St. Lawrence Hospital, Chepstow, for his help in preparation of the manuscript.

References

1. Enneking WF. *Musculoskeletal Surgery*. New York: Churchill Livingstone, 1983.
2. Suit HD, Russell WO, Martin RG. Sarcoma of soft tissue: clinical and histopathological parameters and response to treatment. *Cancer* 1975; **35**: 1478–83.
3. Eilber FR, Mirra JJ, Grant TT, Weisenburger T, Morton DL. Is amputation necessary for sarcomas? A seven-year experience with limb salvage. *Ann Surg* 1980; **192**: 431–7.
4. Karakousis CP, Emrich LJ, Rao U, Krishnamsetty RM. Feasibility of limb salvage and survival in soft tissue sarcomas. *Cancer* 1986; **57**: 484–91.
5. Leibel SA, Tranbaugh RF, Wara WM, Beckstead JH, Bovill EG, Phillips TL. Soft tissue sarcomas of the extremities. Survival and patterns of failure with conservative surgery and postoperative irradiation compared to surgery alone. *Cancer* 1982; **50**: 1076–83.
6. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer* 1981; **47**: 2391–7.
7. Rosenberg SA, Tepper J, Glatstein E *et al.* The treatment of soft-tissue sarcomas of the extremities: prospective randomised evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg* 1982; **196**: 305–15.
8. Davidson T, Westbury G, Harmer CL. Radiation-induced soft-tissue sarcoma. *Br J Surg* 1986; **73**: 308–9.
9. Shiu MH, Castro EB, Hajdu SI, Fortner JG. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. *Ann Surg* 1975; **182**: 597–602.
10. Davidson T, Cooke J, Parsons C, Westbury G. Pre-operative assessment of soft tissue sarcomas by computed tomography. *Br J Surg* 1987; **74**: 474–8.
11. Tepper JE, Suit MD. Radiation therapy alone for sarcoma of soft tissue. *Cancer* 1985; **56**: 475–9.
12. Mantravadi RVP, Trippon MJ, Patel MK, Walker MJ, DasGupta TK. Limb salvage in extremity soft tissue sarcoma: combined modality therapy. *Radiology* 1984; **152**: 523–6.
13. Eilber FR, Guiliano AE, Huth J, Mirra J, Morton DL. High-grade soft-tissue sarcomas of the extremity: UCLA experience with limb salvage. In *Primary Chemotherapy in Cancer Medicine*, *Prog Clin Biol Res* 1985; **201**: 59–74.
14. Imparato AM, Roses DF, Francis KC, Lewis MM. Major vascular reconstruction for limb salvage in patients with soft tissue and skeletal sarcomas of the extremities. *Surg Gynecol Obstet* 1987; **147**: 891–6.
15. Steed DL, Peitzman AB, Webster MW, Ramasastry SS, Goodman MA. Limb sparing operations for sarcomas of the extremities involving critical arterial circulation. *Surg Gynecol Obstet* 1987; **177**: 493–8.
16. Millesi H. Nerve grafting. In: Converse JM, ed. *Reconstructive Plastic Surgery (the Hand and Upper Extremity)*, 2nd edition. Philadelphia: WB Saunders, 1977: 3227–42.
17. Malawer MM, Sugarbaker PH, Lampert M, Baker AR, Gerber NL. The Tikhoff-Linberg procedure: report of ten patients and presentation of a modified technique for tumors of the proximal humerus. *Surgery* 1985; **97**: 518–28.
18. Gherlinzoni F, Bacci G, Picci P *et al.* A randomised trial for the treatment of high-grade soft-tissue sarcomas of the extremities: preliminary observations. *J Clin Oncol* 1986; **4**: 552–8.
19. Markhede G, Nistor L. Strength of plantar flexion and function after resection of various parts of the triceps surae. *Acta Orthop Scand* 1979; **50**: 693–7.
20. Markhede G, Stener B. Function after removal of various hip and thigh muscles for extirpation of tumours. *Acta Orthop Scand* 1981; **52**: 373–95.
21. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft tissue tumours. *Cancer* 1982; **49**: 1721–33.
22. Galli A, Berrino P, Rainero ML, Santi P. Present day role of plastic surgery in management of chronic radiation wounds: our experience. *Eur J Surg Oncol* 1987; **13**: 239–46.
23. Arnold PG, Pairolero PC. Chest wall reconstruction. Experience with 100 consecutive patients. *Ann Surg* 1984; **199**: 725–32.
24. Shiu MH, Flancbaum L, Hajdu SI, Fortner JG. Malignant soft-tissue tumours of the anterior abdominal wall. *Arch Surg* 1980; **115**: 152–5.
25. Suit HD, Mankin HJ, Wood WC, Proppe KH. Preoperative, intraoperative and postoperative radiation in the treatment of primary soft tissue sarcoma. *Cancer* 1985; **55**: 2659–67.
26. Giuliano AE, Eilber FR. The rationale for planned reoperation after unplanned total excision of soft-tissue sarcomas. *J Clin Oncol* 1985; **3**: 1344–8.

Paper accepted 7 March 1988

Br. J. Surg. 1988, Vol. 75, August, 779–781

Assessment of the analgesic efficacy of nefopam hydrochloride after upper abdominal surgery: a study using patient controlled analgesia

T. T. C. McLintock[†], G. N. C. Kenny[*], J. C. Howie, C. S. McArdle[*], S. Lawrie and H. Aitken

Department of Anaesthesia, Victoria Infirmary, Glasgow, and
[*]University Departments of Anaesthesia and Surgery, Glasgow Royal Infirmary, Glasgow G31 2ER, UK
Correspondence to:
Dr G. N. C Kenny, Department of Anaesthetics, Stobhill General Hospital, Glasgow G21 3UW, UK

A randomized, double-blind, placebo-controlled study was performed to assess the analgesic efficacy of intramuscular nefopam hydrochloride after upper abdominal surgery. Patients received either 20 mg nefopam (n = 23) or matching placebo (n = 26), 90 min before surgery, immediately after surgery, and 6, 12 and 18 h after the end of surgery. The 24-h morphine requirements were measured using a patient-controlled analgesia system delivering on-demand intravenous bolus doses of morphine. Pain was assessed using visual analogue scales. Patients receiving nefopam had a mean (±s.e.m.) cumulative morphine consumption of $4{\cdot}1 \pm 0{\cdot}8$ *mg in the first hour, compared with* $8{\cdot}5 \pm 0{\cdot}8$ *mg in the control group* ($P<0{\cdot}01$)*. After 24 h the consumptions were* $44{\cdot}1 \pm 7{\cdot}2$ *mg and* $62{\cdot}5 \pm 6{\cdot}9$ *mg respectively* ($P<0{\cdot}05$)*. The pain scores in both groups were similar. This study confirms that nefopam hydrochloride has significant analgesic effects and would be a useful supplement to morphine in the management of postoperative pain.*

Keywords: Patient-controlled analgesia, postoperative analgesia, morphine, nefopam, morphine-sparing effect

Nefopam hydrochloride is an analgesic agent which is structurally related to diphenhydramine, but has no antihistaminic effects[1]. Its exact mode of action is unclear; it does not bind to opioid receptors and does not cause respiratory depression[2]. Inhibition of prostaglandin biosynthesis occurs only at very high concentrations[3], and the drug does not cause gastrointestinal blood loss[4]. Previous studies comparing nefopam and morphine have reported relative potencies varying from 0·2 to 0·6:1 (nefopam:morphine)[1]. Nefopam is available in both oral and intramuscular forms. The standard intramuscular dose of nefopam is 20 mg at 6-hourly intervals.

Patient-controlled analgesia (PCA) provides good pain relief and is also an accurate method of measuring the morphine requirements of patients after surgery[5]; PCA can therefore be used to measure the efficacy of analgesic agents[6–8]. The PCA system used in this study was developed specifically for this purpose; patient interaction with the system was recorded on magnetic disc[9]. The morphine-sparing effect of an analgesic under study can be estimated by comparing the amount of morphine used by two groups, one receiving an active analgesic and the other a placebo[6,7].

The aim of the present study was to measure the morphine-sparing effect of intermittent intramuscular nefopam in patients with postoperative pain after upper abdominal surgery

Patients and methods

Fifty-three patients, aged 18–75 years, scheduled for elective upper abdominal surgery entered this double-blind study All patients gave informed written consent after reading an information sheet explaining the study, which was approved by the hospital ethics committee. All were American Society of Anesthesiologists class 1–3, and no patient with evidence of renal, hepatic, cardiovascular or respiratory impairment was included Patients with a history of epilepsy or glaucoma, and those receiving analgesic drugs pre-operatively, were also excluded. Patients were shown how to complete linear analogue pain charts and instructed pre-operatively in the use of the PCA system.

Patients were allocated randomly to one of two groups and were premedicated with oral temazepam 90 min before surgery The dose varied according to the patient's weight. 20 mg if <55 kg, 30 mg if <75 kg, and 40 mg if ≥ 75 kg. At this time, patients in the nefopam group were given nefopam 20 mg intramuscularly, and those in the placebo group received a matching placebo.

Anaesthesia was induced with a sleep dose of thiopentone, tracheal intubation was facilitated with vecuronium 0·1 mg/kg, or suxamethonium if indicated, and morphine 0·15 mg/kg was given for analgesia. Anaesthesia was maintained with nitrous oxide in 33 per cent oxygen, and 0·5–1·5 per cent enflurane as required. Increments of vecuronium were given as required. At the end of surgery, neuromuscular block was antagonized with neostigmine 2·5 mg and atropine 1·2 mg.

On arrival in the recovery area, patients were given a second intramuscular dose of either nefopam 20 mg or placebo, and the PCA system was connected to the patient's intravenous infusion via a valved Y-connector[10] The PCA system was set to deliver a bolus dose of morphine 0·02 mg/kg The lockout time was 2 min plus the infusion time of 40 s per mg morphine After they had fully recovered from the anaesthetic and could use the PCA without prompting, patients were transferred to the ward together with the PCA system and received further doses of nefopam or placebo at 6, 12, and 18 h postoperatively. Pain scores were recorded, using a 100 mm linear analogue scale, at 6 and 24 h postoperatively[11,12].

After 24 h, the PCA system was disconnected and the patients were questioned about any adverse effects The nursing staff also recorded any adverse effects, such as episodes of nausea and vomiting, and whether anti-emetics were required The total morphine requirement of each patient in the 24 h was recorded.

Statistical analysis of demographic data was performed using, where appropriate, the unpaired t test or the χ^2 test Non-parametric data were analysed using the Mann–Whitney U test. Statistical significance was taken at $P<0{\cdot}05$.

Results

Of the 53 patients entered into the study, 4 were withdrawn. One patient was returned to theatre from the recovery area; two

Table 1 *Demographic data for nefopam and placebo groups*

	Nefopam ($n=23$)	Placebo ($n=26$)
Male:female	7:16	11:15
Age (years)	49±3·1	46±3·3
Weight (kg)	62·5±2·9	64·4±2·3
Height (cm)	163·3±2·1	167·5±1·9

Values are mean±s.e.m.

Table 2 *Cumulative morphine consumption (mg) at 1 h and 24 h postoperatively*

	Nefopam ($n=23$)	Placebo ($n=26$)
1 h	4·1±0·8	8·5±0·8**
24 h	44·1±7·2	62·5±6·9*

Values are mean±s.e.m. **$P<0·01$; *$P<0·05$ (nefopam *versus* placebo)

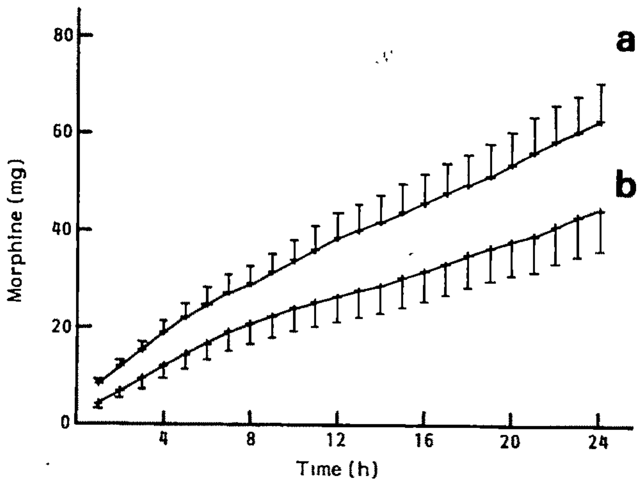


Figure 1 *Mean (s.e.m.) cumulative morphine consumption in milligrams over 24 h for* **a** *placebo and* **b** *nefopam groups*

patients did not have upper abdominal incisions; and one patient was found subsequently to have received buprenorphine the night before surgery. The results from 49 patients were therefore available for analysis.

Both groups were comparable for age, weight, height and sex (*Table 1*). The mean morphine consumption after 1 h and the cumulative morphine consumption after 24 h were significantly lower in the nefopam group ($P<0·01$ and $P<0·05$), as shown in *Table 2*. After the first hour the nefopam group continued to use less morphine, but the differences in the hourly consumptions were not significant. *Figure 1* shows the mean cumulative morphine consumptions of the two groups. Patients in the nefopam group used 50 per cent less morphine than the placebo group in the first hour, and at the end of 24 h had used nearly 30 per cent less than the placebo group. The mean (±s.e.m.) time between the first dose given with the premedication and the second dose given immediately after surgery was 211±12·1 min in the nefopam group and 194±7·8 min in the placebo group (not significant). *Table 3* shows the results of the pain scores: there were no significant statistical differences between the two groups but there was a significant reduction in the scores in each group between 6 and 24 h ($P<0·01$).

The frequencies of side-effects are shown in *Table 4*. Although there was an increased observed occurrence of sweating in the nefopam group ($P<0·01$), none of the patients was aware that they were sweating. Two patients, one in each group, had the size of their bolus dose of morphine reduced by 25 per cent because of nausea. No episodes of respiratory depression were detected, and no patient required a reduction in the bolus dose because of excessive sedation.

Discussion

PCA is an excellent device for assessing the amount of pain a patient is experiencing[5–7]. In general, the more pain a patient experiences the more morphine will be demanded from the PCA system. Unlike pain-scoring methods, the patient does not have to try to assess his own pain, he merely has to press a button if he feels pain. Because the patient is free to use the system whenever he chooses, this technique removes the effect of observer bias. PCA can be used to assess the morphine-sparing effects of any non-opioid analgesic and any pure agonist opioid, given by any route. For obvious reasons, it is not suitable for the assessment of partial agonist drugs.

Previous single-dose studies comparing parenteral nefopam with morphine have shown that nefopam can be equi-analgesic with morphine. However, the results are variable, with relative potencies of nefopam:morphine ranging from 0·3 to 0·6:1[13–16]. Other studies have described an apparent ceiling effect with increasing doses of nefopam[17,18]. This study has shown that nefopam hydrochloride 20 mg when given as part of the premedication and immediately after surgery reduces by 50 per cent the morphine requirements of patients in the first hour after surgery. When given at 6-hourly intervals for postoperative analgesia, nefopam reduces morphine consumption by nearly 30 per cent over 24 h.

The pain score data, which showed no differences between the two groups, demonstrated that both groups had used the PCA to titrate themselves to a similar degree of analgesia. However, the pain scores in both groups were higher at 6 h than at 24 h despite the patients having access to generous amounts of morphine with which to control their pain. A possible explanation could be that the residual effects of anaesthesia reduced their ability to use the PCA system optimally. Alternatively it could be that their usage of morphine in the early postoperative hours was limited by the onset of side-effects such as nausea or sedation. One patient in the placebo group had pain scores of 100 and 95 at 6 and 24 h respectively, despite taking 92·4 mg morphine during that time. In fact, this patient

Table 3 *Median pain scores at 6 h and 24 h postoperatively*

	Nefopam ($n=23$)	Placebo ($n=26$)
6 h	34 (0–79)	38 (5–100)†
24 h	20 (0–66)*	22 (0–95)†*

Patients recorded pain scores on 100 mm linear analogue charts. The median and range of pain scores in millimetres are given. *$P<0·01$ (6 h *versus* 24 h scores); † not significant (nefopam *versus* placebo)

Table 4 *Frequency of side-effects*

	Nefopam ($n=23$)	Placebo ($n=26$)
Nausea	7	9
Vomiting	2	4
Sweating	4	1*

*$P<0·01$ (nefopam *versus* placebo)

appeared to be very comfortable but complained of severe pain when asked.

Despite numerous shortcomings, the most popular method of providing postoperative analgesia is still intermittent intramuscular opioids[19]. One reason that this method is unsatisfactory is that many patients do not receive enough opioid because of fears of respiratory depression. Nefopam does not cause respiratory depression; no episodes of respiratory depression were detected in our patients receiving nefopam and morphine in combination Therefore the combination of standard intermittent doses of nefopam and morphine might be a safe way of increasing the percentage of patients who receive good postoperative analgesia.

The high level of morphine sparing in the first postoperative hour is interesting and was not found in our previous studies using the PCA system to evaluate the effect of analgesic agents in the postoperative period[6,7]. Presumably the morphine-sparing effect is related to the administration of two doses of nefopam within 4 h, the first given at the time of premedication and the second on admission to the recovery area, thereby ensuring high blood levels within the immediate postoperative period. The morphine-sparing effect subsequently fell, suggesting that the 6-hourly dosage regimen may not have been optimum

In summary, we have found that intermittent intramuscular nefopam has a morphine-sparing effect of about 30 per cent in patients during the first 24 h after abdominal surgery. It may be that a 4-hourly dosage regimen would further increase this effect. The combination of standard intermittent intramuscular doses of morphine plus nefopam would ensure that more patients received satisfactory analgesia in the postoperative period without increased risk of opioid-related side-effects.

Acknowledgements

We would like to thank the nursing staff of the recovery area at the Victoria Infirmary, our anaesthetic and surgical colleagues, and Miss McPherson of the Pharmacy Department

References

1. Heel RC, Brodgen RN, Pakes GE, Speight TM, Avery GS Nefopam. a review of its pharmacological properties and therapeutic efficacy *Drugs* 1980; **19**: 249–67
2. Steen SN, Smith R, Kuo J, Mok MS, Lippmann M Effects of nefopam and pentazocine on the human respiratory center *IRCS Med Sci* 1977; **5**: 490
3. Conway AC, Mitchell CL Analgesic studies with nefopam hydrochloride. *Arch Int Pharmacodyn Ther* 1977; **226** 156–71
4. Baltes BJ. Gastrointestinal blood loss study with a new analgesic compound: nefopam hydrochloride. *J Clin Pharmacol* 1977, **17** 120–4.
5. Sechzer PH Objective measurement of pain. *Anesthesiology* 1968; **29**: 209–10.
6. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS The morphine sparing effect of ketorolac tromethamine *Anaesthesia* 1987, **42**. 727–31.
7. Hodsman NBA, Burns J, Blyth A, Kenny GNC, McArdle CS, Rotman H The morphine sparing effects of diclofenac sodium following abdominal surgery *Anaesthesia* 1987, **42** 1005–8.
8. Slowey HF, Reynolds AD, Mapleson WW, Vickers MD Effect of premedication with controlled-release oral morphine on postoperative pain *Anaesthesia* 1985, **40**: 438–40.
9. Gillies GWA, Kenny GNC, McArdle CS A standard microcomputer linked to a volume-controlled infusion pump for patient-controlled analgesia research *J Med Eng Technol* 1986, **10**. 55–7
10. Rosen M, Williams B. The valved-Y-Cardiff Connector (VYCCon). *Anaesthesia* 1979, **34**. 882–4.
11. Huskisson EC. Measurement of pain. *Lancet* 1974; **ii**: 1127–31.
12. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976, **31**: 1191–8
13. Sunshine A, Laska E Nefopam and morphine in man *Clin Pharmacol Ther* 1975; **18** 530–4.
14. Conway M, Lipton S. A comparison of a new analgesic, nefopam hydrochloride, with morphine sulphate, pentazocine and pethidine hydrochloride in post-operative pain. *Curr Med Res Opin* 1982; **7**: 580–97.
15. Mok MS, Lippmann M, Steen SN Comparison of intravenous nefopam versus morphine for the relief of postoperative pain. *Clin Pharmacol Ther* 1979; **25** 237–8.
16. Phillips G, Vickers MDA Nefopam in postoperative pain *Br J Anaesth* 1979, **51**: 961–5
17. Cohen A, Hernandez CM. Nefopam hydrochloride new analgesic agent *J Int Med Res* 1976, **4**: 138–43.
18. Tigestedt I, Sipponen J, Tammisto T, Turunen M Comparison of nefopam and pethidine in postoperative pain. *Br J Anaesth* 1977; **49**: 133–8.
19. Dodson ME A review of the methods for relief of postoperative pain *Ann R Coll Surg Engl* 1982, **64**. 324–7.

Paper accepted 29 March 1988

Br. J. Surg. 1988, Vol. 75, August, 782–785

Prophylactic antibiotics in elective colorectal surgery

W. Y. Lau, K. W. Chu, G. P. Poon and K. K. Ho

Government Surgical Unit, Queen Mary Hospital, Pokfulam Road, Hong Kong

Correspondence to: Dr W. Y Lau, Surgical 'C' Unit, Queen Elizabeth Hospital, Wylie Road, Kowloon, Hong Kong

A randomized prospective study was conducted on 194 patients who underwent elective colorectal surgery for carcinoma. All patients received the same mechanical bowel preparation. In addition, patients in group A received oral neomycin and erythromycin base; patients in group B received systemic metronidazole and gentamicin, while patients in group C received both oral and systemic antibiotics. Postoperative septic complications related to colorectal surgery occurred in 27·4 per cent, 11·9 per cent and 12·3 per cent respectively in groups A, B and C ($\chi^2 = 7$; $P < 0·05$). The incidence of sepsis in groups B and C was almost identical. Patients who received oral antibiotics alone (group A) had significantly higher risks of postoperative sepsis when compared with patients in either group B or group C ($P < 0·05$). As there is no additional advantage of combining oral and systemic antibiotics, we recommend systemic metronidazole and gentamicin to be used with mechanical bowel preparation in elective colorectal surgery.

Keywords: Prophylactic antibiotics, elective colorectal surgery

The judicious use of prophylactic antibiotics, either given orally to obtain a local antimicrobial effect inside the gut lumen, or systemically to increase the tissue resistance to bacterial infection, significantly lowers postoperative septic complications after elective colorectal surgery[1,2].

There is strong evidence to suggest that oral antibiotics effective against aerobic and anaerobic pathogens reduce infection after colectomy[3–5].Oral neomycin and erythromycin base was first proposed by Nichols and associates[4,6,7]. Since then, the regimen has become popular[8] and it is widely used in North America[9]. Its efficacy has been confirmed by many clinical studies[1–4], which include a large multicentre study[3].

On the other hand, many surgeons use short-term prophylactic systemic antibiotics. Although there is still controversy in choosing the ideal systemic antibiotic and in determining the optimal duration of antibiotic administration, many regimens have been shown to be effective in colorectal surgery[1,2].

Thus, it seems logical to compare the efficacy of oral *versus* systemic antibiotics in elective colorectal surgery and to find out whether a combination of these two regimens is better than either alone in a prospective randomized study. For oral antibiotics, we used a standard regimen of oral neomycin and erythromycin base[4,6,7]. For systemic antibiotics, we chose metronidazole and gentamicin because of their proven efficacy[10–12]. No no-treatment control group was used because we considered it unethical[13].

Patients and methods

Patient selection

All patients who underwent elective colorectal surgery for carcinoma in our unit between May 1981 and June 1987 were considered for participation in the study. Patients were excluded if they had inflammatory bowel disease, an existing colostomy, an active infection, a history of sensitivity to any of the antibiotics used, a history of renal insufficiency or eighth nerve dysfunction, an obstructing colonic lesion, or a history of receiving antibiotics within the 2 weeks before operation.

Stratification and randomization

Surgeons were asked to predict pre-operatively the type of operation to be carried out. After informed consent was obtained, patients were stratified into three categories. intraperitoneal ileocolic anastomosis; intraperitoneal colocolic anastomosis; and anterior resection or abdominoperineal 'resection. After stratification all patients were randomly allocated to one of the three treatment groups. A sealed envelope contained the random code number which defined the antibiotic group

Mechanical bowel preparation and antibiotic administration

All patients received mechanical bowel preparation in the manner described by Nichols and associates[6,7] This consisted of a 3-day preparation with diet, oral bisacodyl, oral magnesium sulphate and saline enema.

For patients allocated to group A, 1 gram each of oral neomycin and erythromycin was administered at 1 p.m , 2 p.m and 11 p.m. during the day before operation. For group B patients, metronidazole 500 mg and gentamicin 2 mg per kg body weight were infused intravenously over half an hour just before surgery so that the serum levels of antibiotics were at their peaks at the time of skin incision The systemic antibiotics were repeated at 8-hourly intervals for two more doses. For group C patients, both oral and intravenous antibiotics were given in the manners previously described.

Operative technique

All operations were carried out in the morning. Although maximum latitude in technical details was believed desirable, certain restrictions were imposed to reduce variables. All colonic anastomoses were conducted in two layers, using an open technique, the external seromuscular sutures being of non-absorbable materials and the inner all-layers sutures being of absorbable materials, or the anastomosis was fashioned by a circular anastomosis stapler inserted transanally. Intraperitoneal drains, if used, were brought out through separate stab incisions. Subcutaneous drains were forbidden. A colostomy or mucus fistula should not be brought through the main abdominal incision Fascia was closed with nylon stitches The skin and subcutaneous tissues of the main operative wound were closed in every instance. In abdominoperineal resection, the perineal wound was also closed primarily and a suction drain was routinely brought out through a separate perineal stab wound.

Postoperative observations

All patients were managed by the ward surgeons. All patients with suspected wound or intraperitoneal sepsis were inspected by one independent assessor who did not know which antibiotics were used. Administration of antibiotics, other than the protocol drugs, during the postoperative period was avoided. However, antibiotic therapy was permitted when clinical symptoms and signs suggested the presence of an infection and such findings were recorded before administration of antimicrobial agents. The infection had to be confirmed by appropriate culture findings Possible toxicity of the protocol antibiotics was assessed by pre-operative and regular postoperative haemoglobin measurements, white blood cell counts, electrolytes, urea, creatinine and liver function tests and by the simple

0007–1323/88/080782–04$3 00

Table 1 *Characteristics of patient groups and types of operation*

	Group A (oral)	Group B (systemic)	Group C (oral + systemic)
No. of patients	62	67	65
Age in years (mean ± s.d.)	65·7 ± 12·9	63·5 ± 14·9	62·3 ± 15·7
Male:female	1·4:1	1·3:1	1·3:1
No. of patients with associated serious medical diseases	4	5	5
Types of operation			
Right hemicolectomy	12	14	13
Transverse colectomy	3	4	2
Left hemicolectomy	3	2	2
Sigmoid colectomy	8	7	7
Subtotal colectomy	3	2	5
Pelvic exenteration	0	1	1
Palliative bypass	1	2	1
Anterior resection	14	13	12
Low anterior resection	5	6	6
Abdominoperineal resection	13	16	16

Table 2 *Septic complications directly related to colorectal operations*

	Group A (oral)	Group B (systemic)	Group C (oral + systemic)
No. of patients	62	67	65
Abdominal wound sepsis			
Major	13	4	3
Minor	1	1	0
Perineal wound sepsis			
Major	4	2	2
Minor	0	0	1
Intraperitoneal abscess	3	2	2
Anastomotic dehiscence	1	2	1
Total	22	11	9
No. of patients with complications	17	8	8

clinical assessment of balance and hearing before and after chemotherapy. All patients were examined before discharge from hospital and they were followed up in a specific out-patient clinic at monthly intervals for the first 3 months and thereafter at 2-monthly intervals. All patients were contacted by telephone for follow-up if they failed to attend the follow-up clinic.

Definition of postoperative septic complications

We used the criteria of Ljungqvist, based on the clinical appearance of the wound combined with the results of culture, to determine whether the wounds were infected or clean[14]. Wound infection was defined as wounds with purulent discharge. Wounds with serous discharge which gave positive bacteriological cultures and wounds with serous discharge after the patients had returned home so that cultures could not be taken were also included in the infected group.

Intraperitoneal abscesses were diagnosed by ultrasonic evidence of an abscess, by laparotomy or by spontaneous discharge of pus into the rectum.

Fever of unknown origin was defined as persistent postoperative pyrexia with a daily peak temperature over 38°C for over 5 days and for which a specific focus could not be located.

Post-randomization exclusion

Patients in whom the protocol was violated and patients in whom clinical evidence of septic complications were absent but the original wounds were not available for observation for at least 7 days because of early reoperation or death were excluded.

Estimated sample size

Based on available published reports, infection rates of 20 per cent (range 8–41 per cent) with oral neomycin and erythromycin base[1,3,4,9,15], 8 per cent (range 5–10 per cent) with systemic metronidazole and gentamicin[10–12], and an estimated 4 per cent for patients receiving both oral and systemic antibiotics were projected. An alpha risk of 0·05 and a beta risk of 0·20 were accepted. The initial study was projected to require 200 patients to show a statistical difference. We analysed our results statistically after inclusion of the first 202 patients.

Statistical analysis

Whenever feasible, Student's t test or the χ^2 test was employed for statistical evaluation. Data were significant when $P < 0{\cdot}05$.

Results

Post-randomization exclusion

Eight patients were excluded from this study after randomization: four from group A, one from group B and three from group C. The reasons for exclusion were violation of study protocol in four patients, death from cardiopulmonary causes in three patients and early reoperation for a burst abdominal wound in one patient.

Matching of the groups

Of the 194 evaluable patients, 62 were in group A, 67 in group B and 65 in group C. The randomized groups were well matched with respect to patient characteristics and surgical procedures (*Table 1*).

Sepsis related to colorectal surgery

Postoperative septic complications directly related to colorectal operations are shown in *Table 2*. Sepsis developed in 27·4 per cent in group A, 11·9 per cent in group B and 12·3 per cent in group C ($\chi^2 = 7{\cdot}0$, $P < 0{\cdot}05$). The incidence of sepsis in groups B and C was almost identical. Significantly more patients had septic complications in group A when compared with patients in either group B or group C ($P < 0{\cdot}05$).

Unrelated sepsis

Sepsis unrelated to colorectal operations occurred in 31 patients. This included urinary tract infection in 14 patients, pulmonary infection in 13 patients and venous catheter sepsis in four patients. These complications were evenly distributed in the three groups of patients and there was no statistical difference between them.

Fever of unknown origin occurred in three patients in group A, one in group B and one in group C. All these patients responded clinically to a course of systemic antibiotics effective against aerobes and anaerobes.

Hospital stay

The hospital stay for patients in groups A, B and C (mean ± s.d.) was 14·3 ± 7·2 days, 11·8 ± 6·4 days and 12·1 ± 4·9 days respectively. With this sample size, the difference between the different groups is not statistically significant.

Complications of antibiotic preparation

There was no clinical evidence of ototoxicity or nephrotoxicity in any of the patients who received aminoglycosides in this study. No patient developed pseudomembranous enterocolitis.

Pathogenic organisms

For the 33 patients with postoperative sepsis, pathogenic organisms were isolated in 30 patients (90·9 per cent). The commonest organisms isolated, either in pure or mixed cultures, were *Escherichia coli* (20 patients), *Bacteroides fragilis* (19 patients), *Staphylococcus aureus* (7 patients), *Proteus* species (6 patients), *Streptococcus faecalis* (5 patients) and *Klebsiella* species (3 patients). Although most of the Gram-negative rods were sensitive to gentamicin or neomycin, only 60 per cent of *S. faecalis* and 57 per cent of *S. aureus* were sensitive to erythromycin. All *B. fragilis* isolated were sensitive to metronidazole but only 32 per cent were sensitive to erythromycin.

Discussion

The incidence of septic complications following colorectal surgery is influenced by the pathology of the disease and the type of operation[16]. It is more common following resection for inflammatory bowel diseases than carcinoma. In order to minimize this variable, we studied a homogeneous group of patients with colorectal carcinoma alone. As right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection and abdominoperineal resection differ quite significantly in their incidences of postoperative sepsis[16], we stratified our patients into three different categories before randomization, to make subsequent statistical analysis of the data clinically more relevant[17].

In clinical trials comparing oral with parental antibiotics, results have been conflicting[1,2,18]. Some studies have demonstrated no statistical difference in incidence of postoperative septic complications between oral and systemic antibiotics[19–21]. Other studies have shown the oral route to be superior[8,22–24]; others, the parenteral route[9,25]. These conflicting results are not surprising, as many different oral and systemic antibiotic regimens were used in these studies.

Oral neomycin and erythromycin base have been shown to be one of the most effective oral antibiotic regimens in colorectal surgery[1,2]. Bacteriological study showed this regimen to reduce significantly the concentration of aerobes and anaerobes in the lumen of the colon[4]. It has been well studied clinically[1–4,8,9,15] and it has become popular[8] and widely used[9]. Randomized prospective studies to compare oral neomycin and erythromycin with systemic antibiotics, however, also gave conflicting results[9,24]. Systemic metronidazole and gentamicin were found to be inferior[24] whereas systemic metronidazole and ceftriaxone were superior[9] to oral neomycin and erythromycin. Both these studies can be criticized because the mechanical bowel preparations used differ from that recommended by Nichols and associates[4,6,7]. Furthermore, in one study erythromycin stearate, which is more readily absorbed through the gastrointestinal tract than erythromycin base, was used[24]. Our results, using the standard regimen of oral neomycin and erythromycin base, show systemic metronidazole and gentamicin to be superior.

The use of both oral and systemic antibiotics with mechanical bowel preparation is commonly practised by surgeons in elective colorectal surgery[8]. A few studies have addressed the issue of whether this combined approach is efficacious or unwarranted[18,26,27]. These studies showed no additional benefit by adding oral antibiotics to systemic antibiotics when compared with systemic antibiotics alone[18,26], or when compared with oral antibiotics alone[27]. Our results show that there is no additional advantage of combining oral and systemic antibiotics when compared with systemic antibiotics alone. We therefore recommend systemic metronidazole and gentamicin to be used for prophylaxis against postoperative septic complications in elective colorectal surgery.

Acknowledgements

We thank Dr Corinna Har and Mrs Sylvia Hulse for their help in preparing this manuscript

References

1. Di Piro JT, Bivins BA, Record KE, Bell RM, Griffen WO Jr. The prophylactic use of antimicrobials in surgery. *Curr Probl Surg* 1983; **20**: 76–132.
2. Menaker GJ. The use of antibiotics in surgical treatment of the colon *Surg Gynecol Obstet* 1987; **164**. 581–6.
3. Clarke JS, Condon RE, Bartlett JG *et al* Preoperative oral antibiotics reduce septic complications of colon operations: results of a prospective, randomized, double-blind clinical study. *Ann Surg* 1977; **186**: 251–9.
4. Nichols RL, Brodio P, Condon RE *et al.* Effect of preoperative neomycin–erythromycin intestinal preparation on the incidence of infectious complications following colon surgery. *Ann Surg* 1973; **178**: 453–62.
5. Washington JA, Dearing WH, Judd ES, Elveback JR. Effect of preoperative antibiotic regimen on development of infection after intestinal surgery. prospective, randomized, double-blind study. *Ann Surg* 1974; **180** 567–72
6. Nichols RL, Gorbach SL, Condon RE. Alternation of intestinal microflora following preoperative mechanical preparation of the colon *Dis Colon Rectum* 1971; **14**: 123–7.
7. Nichols RL, Condon RE. Preoperative preparation of the colon. *Surg Gynecol Obstet* 1971; **132**: 323–37.
8. Condon RE, Bartlett JG, Nichols RL, Schutte WJ, Gorbach SL, Ochi S. Preoperative prophylactic cephalothin fails to control septic complications of colorectal operations: results of controlled clinical trial *Am J Surg* 1979, **137**: 68–74
9. Weaver M, Burdon DW, Youngs DJ, Keighley MRB Oral neomycin and erythromycin compared with single-dose systemic metronidazole and ceftriaxone prophylaxis in elective colorectal surgery. *Am J Surg* 1986; **151**: 437–42.
10. Johnston D. Bowel preparation for colorectal surgery. *Br J Surg* 1987; **74**: 553–4
11. Feathers RS, Sagor GR, Lewis AAM, Amirak ID, Noone P Prophylactic antibiotics in colorectal surgery. *Lancet* 1977; **ii**: 4–8.
12. Marti MC, Auckenthaler R. Antibiotic prophylaxis in large bowel surgery: results of a controlled clinical trial *Surgery* 1983; **93**: 190–6.
13. Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H Jr, Fagerström RM. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment control *N Engl J Med* 1981, **305**: 795–9.
14. Ljungqvist U. Wound sepsis after clean operations *Lancet* 1964, **i**: 1095–7
15. Brass C, Richards GK, Ruedy J *et al.* The effect of metronidazole on the incidence of postoperative wound infection in elective colon surgery. *Am J Surg* 1978; **136**: 91–6.
16. Keighley MRB, Burden DW. *Antimicrobial Prophylaxis in Surgery*, 1st edn. Bath. Pitman Press, 1979: 59–104.
17. Berger SA, Nagar H, Weitzman S. Prophylactic antibiotics in surgical procedures. *Surg Gynecol Obstet* 1978, **146**. 469–75.
18. Mechigan D, Zuidema GD, Cameron JL The role of systemic antibiotics in operations upon the colon. *Surg Gyncecol Obstet* 1981; **153**: 573–6.
19. Dion YM, Richards GK, Prentis JJ *et al.* The influence of oral versus parental metronidazole on sepsis following colon surgery. *Ann Surg* 1980; **192**: 221–6.
20. Lewis RT, Allan CM, Goodall RG *et al.* Antibiotics in surgery of the colon. *Can J Surg* 1978; **21**: 339–41.
21. Higgins AF, Lewis A, Noone P *et al.* Single and multiple co-trimoxazole and metronidazole in colorectal surgery. *Br J Surg* 1980; **67**: 90–2.
22. Lewis RT, Allan CM, Goodall RG *et al.* Preventing anaerobic infection in surgery of the colon. *Can J Surg* 1981; **24**: 139–41.
23. Edmondson HT, Rissing JP Prophylactic antibiotics in colon surgery. Cephaloridine versus erythromycin and neomycin. *Arch Surg* 1983; **118**: 227–31

24. Figueras-Felip J, Lara-Eisman F, Caride-Garcia P *et al*. Oral is superior to systemic antibiotic prophylaxis in operations upon the colon and rectum. *Surg Gynecol Obstet* 1984; **158**: 359–62.
25. Keighley MRB, Arabi Y, Alexander-Williams J *et al*. Comparison between systemic and oral antimicrobial prophylaxis in colorectal surgery. *Lancet* 1979; **i**: 894–7.
26. Hanel KC, King DW, McAllister ET *et al*. Single dose parental antibiotics as prophylaxis against wound infections in colonic surgery. *Dis Colon Rectum* 1980; **23**: 98–101.
27. Barber M, Hirschberg BC, Rice CL, Atkins CC. Parental antibiotics in elective colon surgery? A prospective, controlled clinical study. *Surgery* 1979; **86**: 23–9.

Paper accepted 10 April 1988

Case report

Br. J. Surg. 1988, Vol. 75, August, 785

Pre-operative diagnosis of non-strangulated obturator hernia: the contribution of herniography

L. A. Carriquiry and A. Piñeyro

Clínica Quirúrgica 2, Hospital Maciel, Facultad de Medicina, Montevideo, Uruguay

Correspondence to: Dr L. A. Carriquiry, Rafael Pastoriza 1451 ap. 502, Montevideo, Uruguay

Clinical diagnosis of an obturator hernia is elusive. With few exceptions, this uncommon condition has been an unexpected finding during surgical exploration of an intestinal obstruction of uncertain aetiology[1]. Herniography in obscure groin pain, as described by Scandinavian authors[2–5], may improve diagnosis.

Case report

A 78-year-old thin lady had been treated surgically for a right crural hernia 5 years ago. Without noticing any recurrence during the preceding year, she had experienced three acute episodes of intense right groin pain, associated with abdominal cramps, high-pitched bowel sounds and vomiting, which subsided spontaneously within hours. Physical examination showed no signs of groin swelling.

Suspecting an obturator hernia, herniography was performed following the technique described by Gullmo *et al.*[5] and revealed a right obturator hernia (*Figure 1*).

The patient was operated through a preperitoneal approach and a thin peritoneal sac was found intruding into the right obturator foramen. It was freed and resected and a polypropylene mesh was placed beneath the pubis and both obturator foramina.

The postoperative course was uneventful and 1 year after surgery the patient is leading a normal life.

Discussion

Obturator hernia occurs in the older age groups, predominating in the eighth decade, and mainly in women. The inextensible walls of the obturator canal make strangulation common and increase operative risk, because late diagnosis and treatment frequently lead to the finding of a necrotic bowel and make resection mandatory[6]. Therefore a precise pre-operative diagnosis made electively allows a planned surgical approach and an adequate repair. A purely clinical diagnosis is difficult, although it must be suspected whenever acute episodes of groin pain occur in old patients, with absence of groin tumours. Confirmation is possible only when any of the two pathognomonic signs are present: radiation of pain to the medial side of the thigh (Hownship–Romberg sign) or palpation of a painful tumour on vaginal examination. Both are uncommon: Gray *et al.*[1] found the former only in 48 per cent of their patients and the latter in 20 per cent. Herniography has been suggested as a useful method to establish the pre-operative diagnosis. It is a technically simple, easily accessible, minimally invasive and quite inexpensive procedure. Once the hernia is demonstrated, an elective repair must not be delayed, because it allows optimal surgical management, which includes a preperitoneal approach and placement of a synthetic mesh without unnecessary intraperitoneal surgery. On the other hand, emergency surgery due to strangulation makes a laparotomy mandatory because of uncertain diagnosis and commonly leads to resection, with the inadvisability of using a synthetic mesh to repair the defect.

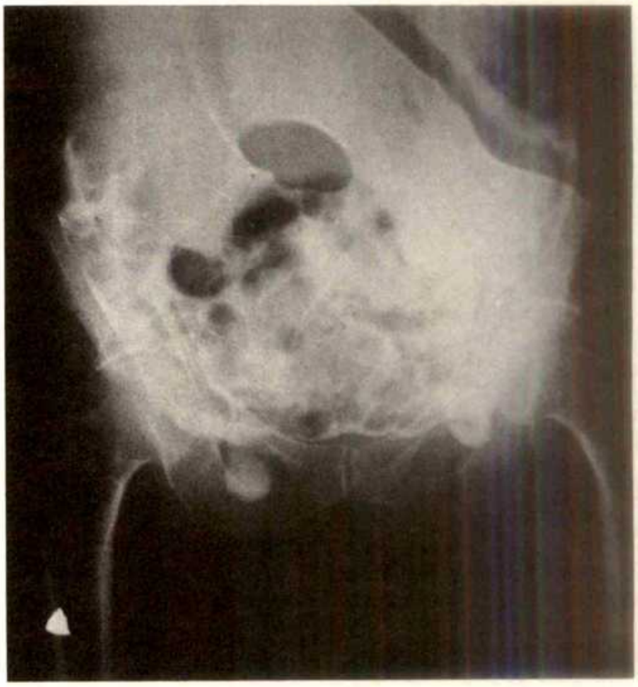


Figure 1 *A contrast-filled pear-shaped peritoneal sac is seen protruding through the right obturator foramen*

References

1. Gray SW, Skandalakis JE, Soria RE, Rowe JS. Strangulated obturator hernia. *Surgery* 1974; **75**: 20–7.
2. Ekberg O. Inguinal herniography in adults: technique, normal anatomy and diagnostic criteria for hernias. *Radiology* 1981; **138**: 31–6.
3. Magnusson J, Gustafson T, Gullstrand P, Holmin T. Herniography—a useful diagnostic method in patients with obscure groin pain. *Ann Chir Gynecol* 1984; **73**: 91–4.
4. Smedberg SGG, Broomé AEA, Elmer O, Gullmo A. Herniography in the diagnosis of obscure groin pain. *Acta Chir Scand* 1985; **151**: 663–7.
5. Gullmo A, Broomé A, Smedberg S. Herniography. *Surg Clin North Am* 1984; **64**: 229–44.
6. Stoppa R. Les hernies de la paroi abdominale. In: Chevrel JP, ed. *Chirurgie des Parois de l'Abdomen* Heidelberg: Springer-Verlag, 1985: 158–225.

Paper accepted 29 February 1988

0007–1323/88/080785–01$3.00

Br. J. Surg. 1988, Vol. 75, August, 786–788

Delayed external sphincter repair for obstetric tear

S. Laurberg, M. Swash and M. M. Henry

The Sir Alan Parks Physiology Unit, St. Mark's Hospital, City Road, London EC1V 2PS, UK

Correspondence to:
Mr M. M. Henry

In some patients with faecal incontinence due to an obstetric tear of the external anal sphincter there is additional weakness of the anal sphincter muscles from damage to the innervation of these muscles during delivery. Of 19 patients who required surgical repair of an obstetric sphincter tear some months or years after injury, 9 (47 per cent) had evidence of pudendal nerve damage at pre-operative anorectal physiological investigation. The result of surgical repair was excellent or good in eight of the ten patients in whom there was no evidence of nerve damage, while this was the case in only one of the nine patients with nerve damage. These results are significantly different ($P = 0{\cdot}018$)*. Thus the functional result of delayed anal sphincter repair after obstetric lesions is partly dependent upon whether the nerve supply is intact. Pre-operative physiological evaluation can give information on the probability of a successful surgical result.*

Keywords: Faecal incontinence, obstetric sphincter tear, anorectal physiology

In recent years it has been shown that vaginal delivery can cause damage to the innervation of the muscles of the pelvic floor, and that this occurs especially with complicated deliveries, when the second stage of labour is prolonged, during delivery of a large baby, or with forceps delivery[1,2]. Moreover, in patients with idiopathic anorectal incontinence in whom there is weakness of the anal sphincter muscles without a localized sphincter defect, there is often a history of difficult labour. In about 80 per cent of these patients there is electrophysiological evidence of damage to the nerve supply of the sphincter muscles, with slowed conduction in the peripheral parts of the pudendal nerves[3,4] and electromyographic evidence of denervation and re-innervation of the muscle fibres[5,6].

Vaginal delivery can also result in direct injury to the anterior parts of the anal sphincter, leading to incontinence[7]. Snooks *et al.*[8] found that there was physiological evidence of damage to the innervation of the sphincter musculature in 60 per cent of patients with anorectal incontinence and an obstetric tear of the anal sphincter. It has been suggested that this accompanying nerve damage could be a factor in the poor results of some sphincter repair procedures[9,10].

In this paper we report clinical and electrophysiological findings supporting this suggestion.

Patients and methods

Patients and surgical outcome

We studied 19 consecutive patients (*Table 1*) admitted to St. Mark's Hospital for treatment of anal incontinence following obstetric sphincter tear. Pre-operative physiological investigations had been performed in all these patients[11]. All patients had an anterior anal sphincter defect; this was confirmed both by the lack of concentric needle EMG activity of the anterior sector of the external sphincter at the pre-operative physiology investigation and, later, by surgical exploration. The pre-operative data for seven of the patients have been reported previously[8].

In 18 of the 19 patients the incontinence started immediately after childbirth. Case 17 became incontinent 24 years after the delivery of her sixth child. One patient (case 4) had two unsuccessful attempts at sphincter repair before referral to St. Mark's Hospital. Case 18 had previously had two sphincter repairs and a pelvic floor repair, but incontinence developed 12 years later. Case 9 had an anal operation in infancy, and became incontinent after a forceps delivery. Case 3 was incontinent to flatus of sufficient degree to cause disabling social embarrassment.

Two patients developed a rectovaginal fistula at the site of the primary sphincter repair after childbirth. One was immediately treated with a colostomy (case 5) and the rectovaginal fistula and sphincter defect were repaired simultaneously. In the other (case 6), the fistula had already been treated when she was referred with incontinence. In this patient and in two other cases (cases 4 and 9) the sphincter repair was performed with a temporary colostomy. In all 19 patients the sphincter repair was performed using Parks' overlapping suture technique[7]. In each case surgical repair was considered satisfactory, and there were no postoperative complications. The perineal wound healed by first intention. The postoperative follow-up ranged from 9 months to 3 years.

Grading of pre-operative and postoperative continence

The pre-operative and postoperative continence was graded retrospectively from the case reports using a scale from 1 to 4 (*Table 1*). If the patient had the same grade after surgical repair as before surgery, an assessment was made as to whether the incontinence was similar, less frequent, or more frequent. In all cases grading was performed without knowledge of the pre-operative physiology results.

Outcome of surgery

By comparing the pre-operative and postoperative continence gradings the outcome of surgery was classified as excellent, good, fair or bad (*Table 1*).

Physiological tests (Table 2)

Anal manometry. In all but one patient, maximal resting and squeeze pressures were recorded using standard techniques, as described previously[11].

Pudendal nerve terminal motor latency (PNTML) measurements. In all patients the latencies from transrectal stimulation of the pudendal nerves at the ischial spines to the responses in the external anal sphincter on the two sides were recorded using the method developed at St. Mark's Hospital[2–4,11]. In 18 patients the right and left PNTML was determined from stimulation of each pudendal nerve; in one patient the PNTML could be measured only on the right side (case 15). On the left side in this patient there was no response.

Single-fibre EMG of the external anal sphincter. Single-fibre EMG studies of the external anal sphincter had been carried out pre-operatively in 10 of the 19 patients. The fibre density was calculated using the method previously described from this laboratory[1,2,5,6,11].

Interpretation of physiological tests. An increased PNTML implies slowed conduction in the terminal part of the pudendal nerve innervating the external anal sphincter, while an increase in fibre density is a measure of compensatory re-innervation of the external anal sphincter, following previous partial denervation. Patients were

0007–1323/88/080786–03$3.00

Table 1 *Pre-operative and postoperative clinical information*

Case	Age (years)	Parity	Duration of FI (years)	Pre-operative grade	Postoperative grade	Postoperative follow-up (years)	Outcome of surgery
1	23	1	1	3	1	1·5	Excellent
2*	26	1	3	3	(3)	3	Fair
3*	27	1	4	2	2	1	Bad
4*	29	1	3	4	4	3	Bad
5*	30	1			3	3	Fair
6	31	2	2	3	1	2	Excellent
7*	32	1	1·5	3	(3)	1·5	Fair
8	33	4	2	3	(3)	0·75	Fair
9*	33	2	1·5	4	4	3	Bad
10	33	1	10	3	1	1	Excellent
11	35	1	3	3	2	1	Good
12*	39	2	18	4	1	2	Excellent
13*	43	4	10	3	3	2	Bad
14	44	3	3	4	1	1·5	Excellent
15*	47	2	24	3	(3)	1	Fair
16	47	6	5	4	1	1	Excellent
17	53	2	6	3	1	2	Excellent
18	64	2	3	3	1	1	Excellent
19	64	6	28	3	(3)	0·75	Fair

FI, faecal incontinence; * pudendal neuropathy (*see Table 2*). The pre-operative and postoperative continence was graded thus: grade 4, incontinent to solid stools; grade 3, incontinent to liquid stools; grade 2, incontinent to flatus; grade 1, continent including some control of flatus The postoperative values in parentheses indicate no change in grade after surgery but less frequent episodes of incontinence Outcome of surgery was classified as follows excellent, grade 1 after surgery; good, higher grade after surgery; fair, same grade after surgery but less frequent incontinence; bad, no improvement. Case 5 had a colostomy present when referred

Table 2 *Results of pre-operative anorectal physiology investigations*

Case	Resting pressure (cmH_2O)	Squeeze pressure* (cmH_2O)	Fibre density	PNTML right (ms)	PNTML left (ms)	Pudendal neuropathy
1	50	33	1·6	1·5	1·7	
2	10	40	1·8	1·7	1·7	+
3	35	150		2·6	2·1	+
4	25	30		3·1	3·3	+
5	60	1	2·1		2·5	+
6	35	20	1·7	2·0	1·6	
7	40	2	2·0	2·4	2·5	+
8			1·6	2·4	1·8	
9	40	20	1·8	2·4	3·0	+
10	30	30	1·7	2·0	2·0	
11	20	10		2·6	2·2	
12	48	40		2·6	2·6	+
13	90	20	1·9	1·8	1·8	+
14	38	38		1·8	1·8	
15	117	23		2·7	—	+
16	10	15		2·0	2·1	
17	20	40	1·5	2·4	2·4	
18	51	27		1·8	1·8	
19	40	50		2·4	2·0	

* Squeeze pressure: maximal contraction pressure minus resting pressure; in case 15 no response could be elicited on the left side of the external anal sphincter muscle. PNTML, pudendal nerve terminal motor latency

considered to have neurogenic damage to the external anal sphincter if the PNTML was longer than 2·4 ms on either side and/or the fibre density was greater than 1·7 (reference 11).

Results

Using the criteria described above, nine (47 per cent) of the patients had an excellent or good result following the sphincter repair, six (32 per cent) a fair result and in four (21 per cent) surgery failed to improve continence. Age, parity, duration or severity of the incontinence were not predictive factors in determining the result of surgery.

At the pre-operative physiology investigation nine (47 per cent) of the patients had evidence of damage to the innervation of the external anal sphincter, as shown by an increase in PNTML and/or fibre density.

Table 3 *Outcome of surgery for patients with and without evidence of pudendal nerve damage*

	Outcome*			
Nerve damage	Excellent	Good	Fair	Bad
Present	1	0	4	4
Absent	7	1	2	0

* See Table 1 for a description of the classification of outcome

Outcome in relation to pudendal nerve damage

In *Table 3* the outcome of surgery is recorded separately for patients with and without evidence of damage to the innervation of the external anal sphincter.

Of the 10 patients without evidence of nerve damage, eight (80 per cent) had an excellent or good result from the repair, but only one (11 per cent) of the patients with nerve damage had a good or excellent result. These results are significantly different ($P = 0{\cdot}018$, one-tailed). For this statistical analysis the results in the two groups of patients were divided into excellent/good and fair/bad, and the P value was subsequently calculated using the exact probability test. Additional statistical analysis using the Wilcoxon rank sum test for unpaired data with the patients subdivided into the four subgroups shown in *Table 1* gives $P < 0{\cdot}01$ (two-tailed).

There was no correlation between the outcome of surgery and the pre-operative anorectal manometry studies.

Discussion

In a previous physiological investigation of 20 patients with anorectal incontinence after an obstetric tear of the external anal sphincter muscle, 60 per cent had evidence of damage to the innervation of the sphincter muscles[8]. In the present series, 47 per cent of the patients had evidence of pudendal nerve damage. In general, patients without electrophysiological evidence of pudendal nerve damage had a good or excellent result from surgical repair, but the results in the patients with pudendal nerve damage were much less encouraging. In patients with nerve damage any improvement gained by surgical repair lessens with time due to progression of the nerve damage caused by recurrent traction damage on the pudendal nerves during perineal descent associated with defaecation straining[12]. It is this associated progressive neurogenic damage to the sphincters that leads to the poor outcome in the long term in this group of patients. Nevertheless, in patients with both direct sphincter tears and pudendal nerve damage, the relatively simple procedure of direct overlapping sphincter repair should first be attempted[9]. If the result of this procedure is not satisfactory or there is deterioration later, additional surgery to the pelvic floor, for example a postanal repair[13], may restore continence.

Our results also provide strong support for avoidance of further vaginal delivery after previous anal sphincter injury to the sphincter, and, especially, its innervation[1,2]. In five of our patients there was only slight anorectal incontinence after the delivery in which the sphincter tear occurred, but this problem was greatly aggravated after subsequent vaginal delivery.

Acknowledgements

We thank our surgical colleagues at St. Mark's Hospital for access to their clinical records. Dr S. Laurberg was supported by a grant from the University of Aarhus, Denmark

References

1. Snooks SJ, Setchell M, Swash M, Henry MM Injury to innervation of pelvic floor sphincter musculature in childbirth *Lancet* 1984; **ii**: 546–50.
2. Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. *Int J Colorect Dis* 1986; **1**: 20–24.
3 Kiff ES, Swash M. Normal proximal and delayed distal conduction in the pudendal nerves of patients with idiopathic (neurogenic) faecal incontinence. *J Neurol Neurosurg Psychiatry* 1984; **47**: 820–3.
4. Snooks SJ, Swash M, Henry MM. Abnormalities in central and peripheral nerve conduction in patients with anorectal incontinence. *J R Soc Med* 1985; **78**: 294–300.
5 Neill ME, Swash M Increased motor unit fibre density in the external sphincter muscle in ano-rectal incontinence a single fibre EMG study. *J Neurol Neurosurg Psychiatry* 1980; **43**: 343–7
6 Neill ME, Parks AG, Swash M. Physiological studies of the pelvic floor in idiopathic faecal incontinence and rectal prolapse. *Br J Surg* 1981; **68**: 531–6.
7. Parks AG, McPartlin JF. Late repair of injuries of the anal sphincter. *Proc R Soc Med* 1971; **64**: 1187–9.
8 Snooks SJ, Henry MM, Swash M. Faecal incontinence due to external sphincter division in childbirth is associated with damage to the innervation of the pelvic floor musculature; a double pathology *Br J Obstet Gynecol* 1985; **92**: 824–8.
9. Browning GP, Motson RW Anal sphincter injury. Management and result of Parks' sphincter repair. *Ann Surg* 1984; **99**: 351–7.
10 Motson RW. Sphincter injuries: indications for, and results of sphincter repair. *Br J Surg* 1985; **72** (suppl) 19S–21S
11. Henry MM, Snooks SJ, Barnes PRH, Swash M. Investigation of disorders of the anorectum and colon. *Ann R Coll Surg Engl* 1985; **67**: 355–60.
12. Jones PN, Lubowski DZ, Swash M, Henry MM. Relation between perineal descent and pudendal nerve damage in idiopathic faecal incontinence. *Int J Colorect Dis* 1987, **2**: 93–5.
13. Browning GP, Parks AG. Post anal repair for neuropathic faecal incontinence correlation of clinical result and anal canal pressures. *Br J Surg* 1983; **70**: 101–4.

Paper accepted 27 March 1988

Br. J. Surg. 1988, Vol. 75, August,
789–792

Blood transfusion and infectious complications following colorectal cancer surgery

P. I. Tartter

Department of Surgery, Annenberg 25–60, The Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, N Y 10029, USA
Correspondence to: Dr P I Tartter

Blood transfusion has been linked to clinical phenomena attributable to immune suppression. We prospectively studied the relationship between perioperative blood transfusion and postoperative infectious complications in 343 consecutive patients undergoing surgery for colorectal cancer. Of the 134 patients who received transfusions 33 (24·6 per cent) developed infectious complications compared with 9 (4·3 per cent) of the 209 patients who did not receive blood ($P < 0{\cdot}0001$). *The mean number of units of blood received by patients who developed infectious complications significantly exceeded the number for patients without infectious complications (2·31* versus *0·74,* $P < 0{\cdot}0001$). *The association of transfusion with infections was highly significant* ($P < 0{\cdot}0001$) *after controlling for age, sex, blood loss, procedure, tumour differentiation, stage, admission haematocrit, duration of surgery, length of the specimen and tumour size. Blood transfusion appears to be an independent risk factor for postoperative infectious complications.*

Keywords: Colorectal cancer, blood transfusions, infectious complications, operation

The competence of the immune system may be a significant determinant of morbidity and mortality in the general surgical patient. Pre-operative immune suppression manifested by anergy to skin tests is associated with postoperative infection, septicaemia, and death related to infection[1]. To naturally occurring immune deficiency may be added certain iatrogenic factors inherent in the operative procedure such as anaesthetic agents[2,3], duration of surgery[4], and the magnitude of the procedure[5].

Recently another factor, perioperative blood transfusion, has been implicated in postoperative immune suppression[6]. Numerous studies in organ transplantation have demonstrated prolonged survival of allografts by transfusion-induced immune suppression. In addition, in cancer patients early recurrence and poor prognosis are associated with perioperative blood transfusion and attributed to immune suppression.

These observations lead to speculation that perioperative blood transfusion, by inducing immune suppression, may contribute to postoperative infections and septic mortality. Multivariate studies have found that blood transfusion is an independent risk factor for postoperative infections[7–9] and organ system failure[10]. The current study is our appraisal of the association of perioperative blood transfusion with postoperative infections in patients with colorectal cancer.

Patients and methods

A total of 343 consecutive patients were studied. None had pre-operative evidence of liver or other metastases. Patients were identified pre-operatively between 1 August 1983 and 31 July 1986. All patients received bowel preparation with laxatives, enemas, oral neomycin and erythromycin base, and intravenous cephazolin. Cephazolin was continued for 24 h following surgery. A purulent exudate was accepted as irrefutable evidence of wound infection. Urinary tract infection was diagnosed when culture yielded more than 100 000 pathogens/ml or signs and symptoms of urinary tract infection were present in the absence of other possible sources. Pneumonia was diagnosed by fever, leucocytosis and infiltrate on chest X-ray. Intra-abdominal collections were localized by ultrasonography and by computed tomographic scanning when other studies failed to reveal a source for fever and leucocytosis.

Information was recorded on age, sex, operative procedure, size of tumour, degree of differentiation, number of involved nodes, length of specimen, stage, admission haematocrit, operative blood loss, duration of operation, and blood transfusions administered during hospitalization: pre-, intra-, and postoperatively. No patients received chemotherapy or radiotherapy during the study.

The variables (e.g. age, sex, etc.) of the patients who developed infectious complications were compared with the values for patients who did not develop infectious complications. Student's t and χ^2 tests were used where appropriate. Multivariate analysis of the data was accomplished using BMDP stepwise logistic regression software[11,12] run on an IBM 370 computer housed at the City University of New York Computing Center. This program investigates the relationship between a binary dependent variable such as infectious complication and a set of independent variables which may be categorical (such as operative procedure and sex) or interval-scaled (such as age, operative blood loss, duration of procedure, etc.).

Results

Of the 343 patients studied, 42 (12·2 per cent) developed infections following surgery (*Table 1*). Thirteen patients (3·8 per cent) developed wound infections and six (1·7 per cent) developed intra-abdominal or pelvic collections. Three patients with wound infections subsequently developed dehiscence of the abdominal wound and died with multiple septic complications. One patient with suspected pelvic collection after abdominoperineal resection died from septic shock. Twelve patients had postoperative urinary tract infections which resolved with intravenous antibiotics. All patients in this study were routinely catheterized with indwelling Foley balloon catheters before

Table 1 *Source of infection in the 343 patients studied*

	n	%
Wound	13	3·8
Urine	12	3·5
Abdominopelvic	6	1·7
Pneumonia	6	1·7
Sepsis without source	4	1·2
Phlebitis	1	0·3
Total	42	12·2

Supported by the Frieda and George Zinberg Foundation and NCI-NIH Grant 1 R01-CA-35558-01

0007–1323/88/080789–04$3 00

Table 2 *Comparison of patients with and without infectious complications*

	Infected	Not infected	*P*
Age	70	68	0·254
Sex			
Males	22	151	0·849
Females	20	150	
Operation			
Right hemicolectomy	4	63	0·003
Transverse colectomy	0	10	
Left hemicolectomy	9	33	
Sigmoid resection	11	63	
Anterior resection	2	79	
Anterior resection with colostomy	8	29	
Abdominoperineal resection	7	19	
Subtotal colectomy	1	5	
Admission haematocrit	38·4	38·2	0·842
Specimen length (cm)	30	28	0·444
Duration of surgery (min)	193	172	0·018
Blood loss (dl)	5·7	5·1	0·648
Blood transfusions	2·31	0·74	<0·001
Tumour size (ml)	22·3	19·5	0·317
Nodes	1·6	1·1	0·138
Differentiation			
Well	160	24	0·200
Moderate	101	12	
Poor	17	6	
Dukes' classification			
A	3	38	<0·001
B_1	1	30	
B_2	17	87	
C_1	8	91	
C_2	10	16	
'D'	3	39	

P values are taken to three decimal places

Table 3 *Association of infection with blood transfusion for each operative procedure*

	n	Infections	%
Right hemicolectomy			
Transfused	26	4	15
Not transfused	41	0	0
Transverse colectomy			
Transfused	5	0	0
Not transfused	5	0	0
Left hemicolectomy			
Transfused	21	8	38
Not transfused	21	1	5
Sigmoid resection			
Transfused	19	8	42
Not transfused	55	3	5
Anterior resection			
Transfused	18	1	6
Not transfused	63	1	2
Anterior resection with colostomy			
Transfused	23	7	30
Not transfused	14	1	7
Abdominoperineal resection			
Transfused	16	4	25
Not transfused	10	3	33
Subtotal colectomy			
Transfused	3	1	33
Not transfused	3	0	0

surgery. Six patients (1·7 per cent) developed pneumonia, one of whom also had a cerebrovascular accident and myocardial infarction but recovered and was discharged home. Four patients with fever, leucocytosis and positive blood cultures were successfully treated with intravenous antibiotics without a source of infection being found. For two of these patients colon resection had included a splenectomy for iatrogenic injury. One patient developed septic phlebitis.

Univariate analysis comparing the patients who developed infections and those who remained uninfected (*Table 2*) revealed significant differences in the number of units of blood received, the distribution of the operative procedures, and the duration of surgery. Since progressive stage was not significantly associated with increasing risk of infection and, although significant by χ^2 analysis, was not significant by the multivariate analysis to follow, it is not considered further.

Right hemicolectomies, transverse colon resections, and anterior resections were associated with low risk of infection compared with 16–27 per cent for the remaining procedures. However, transfused patients exhibited greater risk of infection than untransfused patients after every operation with the sole exception of abdominoperineal resections (*Table 3*).

The risk of infection for patients with procedures lasting less than the mean of 174·4 min was 8·3 per cent compared with 16·7 per cent for more lengthy operations ($\chi^2 = 13{\cdot}371$, $P < 0{\cdot}0001$). However, transfusion was significantly related to infection among patients with both short and long operations (*Table 4*).

Blood transfusion was significantly associated with infection because 33 (24·6 per cent) of the 134 patients who received transfusions developed infectious complications compared with nine (4·3 per cent) of the 209 patients who did not receive blood transfusions (*Table 5*). The mean number of blood transfusions among the patients with infectious complications significantly exceeded those among patients without complications (2·31 *versus* 0·74, $P < 0{\cdot}0001$, *Table 2*). The administration of blood was significantly ($P < 0{\cdot}05$) associated with low admission haematocrit, high operative blood loss, bowel penetration by tumour (classification B_2 or greater), poor tumour differentiation, and lengthy specimens. However, none of these factors was associated with infectious complications ($P > 0{\cdot}10$). Blood transfusions were associated with infectious complications when given pre-, intra-, or postoperatively (*Table 5*). None of the transfused patients developed an infectious complication before receiving their first unit of blood. In addition, the risk of postoperative infection increased progressively with the number of units of blood given, from 5 per cent without transfusion to 30 per cent with three or more units of blood.

Table 4 *Association of infection with blood transfusion controlling for duration of procedure*

	n	Infections	%
Long procedures (> 174 min)			
Transfused	78	22	28
Not transfused	84	5	6
Short procedures (< 175 min)			
Transfused	52	11	21
Not transfused	129	4	3

Table 5 *Relationship of infection with blood transfusions given preoperatively, intra-operatively and postoperatively*

	n	Infected	%
Pre-operative			
Transfused	26	5	19
Not transfused	317	37	12
Intra-operative			
Transfused	75	16	21
Not transfused	268	26	10
Postoperative			
Transfused	58	18	31
Not transfused	285	26	9
Overall			
Transfused	134	33	25
Not transfused	209	9	4

Table 6 *Multivariate analysis with infectious complication as the dependent variable*

Variable	χ^2	P	Degrees of freedom
Age	0·16	0·686	1
Sex	<0·01	0·982	1
Operation	10·74	0·150	7
Haematocrit	5·13	0·024	1
Duration of surgery	0·04	0·839	1
Estimated blood loss	0·07	0·790	1
Transfusions	30·54	<0·001	1
Tumour size	0·85	0·356	1
Nodes	2·36	0·125	1
Differentiation	0·18	0·669	1
Dukes' classification	0·96	0·327	5

P values are taken to three decimal places

Multivariate stepwise logistic regression was used to combine variables, beginning with the most significant, into a model which will predict whether or not a patient will develop an infectious complication (*Table 6*). After each variable is added to the model, the significance of the remaining variables is recalculated, variables with $P<0{\cdot}1$ are added and those with $P>0{\cdot}15$ are removed. The result of this analysis is that admission haematocrit and whether or not the patient received blood transfusions were significantly related to the development of infectious complications. Admission haematocrit was significantly related to infection only in the context of transfusion: none of the patients with low admission haematocrits (below the mean of 38·2) developed infectious complications unless they were transfused (*Table 7*). The risk of infection among patients with low admission haematocrit was 11·9 per cent and 12·5 per cent for patients with normal haematocrits.

Finally, we used the multivariate analysis to investigate the relationship of transfusion to infection after consideration of all of the other variables. After consideration of age, sex, blood loss, procedure, tumour differentiation, stage, admission haematocrit, duration of surgery, length of specimen, and tumour size, the association of blood transfusion with infectious complications was highly significant ($\chi^2=18{\cdot}09$, $P<0{\cdot}0001$).

Discussion

This study implicates blood transfusion as a factor in the development of postoperative infectious complications. The temptation is to attribute the association of blood transfusion with infection to operative difficulty or trauma related to the severity of disease and reflected by the need for transfusion. The lack of association of anaemia, stage, blood loss, specimen length and tumour size with infection, and the observation that transfusion was associated with infection independent of the operative procedure and its duration suggest that some other mechanism accounts for this association. In addition, two studies of penetrating abdominal trauma have identified blood transfusion as an independent risk factor for postoperative infections. A prospective multi-institutional study of patients with penetrating abdominal trauma observed that the number of units of blood administered was significantly related to the risk of operative infection independent of the number of organs injured, colostomy formation, increased age, and shock on arrival[7]. A more recent study limited to penetrating colonic injury found that the number of units of blood given was the most significant risk factor for infection ($P=0{\cdot}0004$) and a dose–response relationship existed between the number of units of blood given and the proportion of patients with infections[8]. Shock, age, and number of organs injured were also significant, but colostomy, pre-operative delay, site of injury, duration of surgery, and degree of contamination were not significantly related to infection.

Operative difficulty and disease (or injury) severity are variables that are easily controlled using animal models.

Table 7 *Association of infection with blood transfusion controlling for admission haematocrit*

	n	Infections	%
Low haematocrit (<38·3)			
Transfused	88	19	22
Not transfused	71	0	0
High haematocrit (>38·2)			
Transfused	43	14	33
Not transfused	141	9	6

Allogeneic transfusions of rats are followed by immune suppression[13,14] and increased mortality from burn wound sepsis[16], intraperitoneal injections of *Escherichia coli*[14], and caecal ligation with puncture (D. C. Maidman *et al.*, unpublished results) compared with rats given syngeneic blood. The available animal studies support the hypothesis that blood transfusion-induced immune suppression increases susceptibility to infection and subsequent mortality.

The specific component of transfused blood responsible for immune suppression has not been identified. Red cells and their components are immunosuppressive *in vitro* (references 16 and 17 and Tartter *et al.*, unpublished results), possibly owing to macrophage release of prostaglandin E (reference 18). The reticulo-endothelial system is implicated by the observation that transfused damaged red cells are sequestered by the spleen and increase susceptibility to septic challenge[19]. Transplant studies have implicated leucocytes in the production of the transfusion effect in transplantation[20]. However, since blood storage reduces the number of viable leucocytes and improves renal allograft survival[21], and leucocyte extracts[22] and large volumes of donor-specific serum prolong the survival of skin allografts[23], leucocyte-derived products present in the serum of the transfused blood may be the cause of transfusion-induced immune suppression. Plasma has been implicated in transfusion-associated cancer recurrence by tumour growth experiments in mice[24] and by clinical studies[25].

Unfortunately, it is currently impossible to prove that the observed clinical phenomena in humans are not due to viral contamination of transfused blood. Human cytomegalovirus infections have long been associated with immune suppression[26,27] and post-transplantation infection is common[28]. The facility with which the clinical studies can be reproduced in animal models makes it unlikely that viral infections are the cause of these phenomena.

The effect of blood transfusion on transplants, malignancies and infections, even if all three are mediated by immune suppression, is unlikely to be mediated through the same arm of the immune system Current dogma indicates that malignant cells are destroyed by separate systems from those that destroy bacteria. Some have argued 'before rational strategies can be evolved for minimizing the deleterious effects of blood transfusion, it is essential that these mechanisms be clearly defined'[6]. We do not agree that clinical studies of blood components for surgery should be postponed until the immune system is unravelled. Proof that transfusion affects a given element of the immune system is at hand, but proving that a given element of the immune system is responsible for postoperative infections or recurrent malignancies is difficult.

References

1. MacLean LD, Meakins JL, Taguchi K, Duigan JP, Dhillon KS, Gordon J. Host resistance in sepsis and trauma. *Ann Surg* 1975; **182**: 207–17
2. Tarpley JL, Twomey PL, Catalona WJ, Chretien PB Suppression of cellular immunity by anesthesia and operation *J Surg Res* 1977, **22**. 195–201.
3. Jubert AV, Lee ET, Hersh EM, McBride CM. Effects of surgery, anesthesia and intraoperative blood loss on immunocompetence. *J Surg Res* 1973 **15**: 399–403
4. Roth JA, Golub EA, Grimm BA, Eilber MD, Morton DL. Effects of operation on immune response in cancer patients. sequential

evaluation of in vitro lymphocyte function *Surgery* 1976; **79**: 46–51.

5 Vose BM, Moudgil GC Effect of surgery on tumour-directed leukocyte responses. *Br Med J* 1975; i: 56–8.

6. George CD, Morello PJ. Immunological effects of blood transfusion upon renal transplantation, tumor operations, and bacterial infections. *Am J Surg* 1986, **152**. 329–37.

7. Nichols RL, Smith JW, Klein DB *et al.* Risk of infection after penetrating abdominal trauma. *New Engl J Med* 1984; **311**· 1065–70.

8. Dawes LG, Aprahamian C, Condon RE, Malangoni MA: The risk of infection after colon injury. *Surgery* 1986; **100**. 796–803.

9. Tartter PI, Quintero S, Barron DM. Perioperative blood transfusion associated with infectious complications after colorectal cancer operations *Am J Surg* 1986; **152**: 479–82

10. Maetani S, Nishikawa T, Tobe T, Hirakawa A. Role of blood transfusion in organ system failure following major abdominal surgery *Ann Surg* 1986; **203** 275–81.

11. Engelman L. Stepwise logistic regression. In: Dixon WJ, Chief ed. *BMDP Statistical Software* Berkeley: University of California Press, 1981.

12. Cox, DR *Analysis of Binary Data.* Methuen: London: 1970.

13. Waymack JP, Rapien J, Garnett D, Tweddell JS, Alexander JW. Effect of transfusion on immune function in a traumatized animal model. *Arch Surg* 1986; **121**: 50–5.

14 Waymack JP, Warden GD, Alexander JW, Miskell P, Gonce S. Effect of blood transfusions and anesthesia on resistance to bacterial peritonitis. *J Surg Res* 1987; **42**: 528–35.

15. Waymack JP, Alexander JW. Effect of transfusion on immune function in a traumatized animal model: II. Effect on mortality rate following septic challenge. *Arch Surg* (In press).

16. Keown PA, Descamps B. Improved renal allograft survival after blood transfusion: a nonspecific, erythrocyte-mediated immunoregulatory process? *Lancet* 1979, **i**: 20–2

17. Keown PA, Descamps B. Suppression of the mixed lymphocyte reaction by autologous red cells and their constituents. *C R Acad Sci (III)* 1978; **749**: 287

18 Waymack JP, Gallon L, Barcelli U, Trocki O, Alexander JW. Effect of blood transfusions on immune function III. Alterations in macrophage arachidonic acid metabolism. *Arch Surg* 1987; **122**: 56–60.

19. Grover GJ, Loegering DJ. Effect of splenic sequestration of erythrocytes on splenic clearance function and susceptibility to septic peritonitis. *Infect Immun* 1982; **36**: 96–102

20. Persijn GG, Cohen B, Lansbergen Q, van Rood JJ. Retrospective and prospective studies on the effect of blood transfusions in renal transplantation in the Netherlands. *Transplantation* 1979; **28**: 396–401.

21. Leivestad T, Flatmark A, Hirschberg M, Thors BY Effect of pretransplant donor specific transfusions in renal transplantation *Transplant Proc* 1982; **14**: 370–3.

22. Rapaport FT, Dausset J. Facilitation of skin allograft survival by blood leucocyte extracts. *Ann Surg* 1984; **199**: 79–86

23. Hasek M, Chutna J, Holan V, Sladecek M Induction of transplantation tolerance using serum as antigen source *Nature* 1976; **262**· 295–6.

24. Horimi T, Kagawa S, Ninomiya M, Yoshida E, Hiramatsu S, Orita K Possible induction by blood transfusion of immunological tolerance against growth of transplanted tumors in mice. *Acta Med Okayama* 1983; **37**: 259–63.

25. Blumberg N, Heal JM, Murphy P, Agarwal MM, Chuang C. Association between transfusion of whole blood and recurrence of cancer *Br Med J* 1986; **293**: 530–3.

26 Fiala M, Payne JE, Berne TV *et al.* Epidemiology of cytomegalovirus infection after transplantation and immunosuppression *J Infect Dis* 1975; **132**: 421–33

27. Rand KH, Pollard RB, Merigan TC. Increased pulmonary superinfections in cardiac-transplant patients undergoing primary cytogalovarius infection. *New Engl J Med* 1978; **298**: 951–3.

28. Glenn J. Cytomegalovirus infections following renal transplantation. *Rev Infect Dis* 1981; **3**· 1151–78.

Paper accepted 20 March 1988

The Association of Surgeons in Training

Membership of the Association is open to all Senior Registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are two years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides having scientific and social functions.

If you are not a member please contact the secretary, Andrew McIrvine, 35 Elsie Road, Dulwich, London SE22 8DX, UK, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Belfast on 8–10 September 1988.

Br. J. Surg. 1988, Vol. 75, August,
793–796

Influence of pancreatic resection on systemic complications in acute necrotizing pancreatitis

O. Teerenhovi, I. Nordback and J. Isolauri

Department of Surgery, University Central Hospital of Tampere, 33520 Tampere, Finland

Correspondence to:
Dr O Teerenhovi

The influence of pancreatic resection on early systemic complications of acute necrotizing pancreatitis was evaluated in 84 patients. The aetiology of pancreatitis was alcohol 71 per cent, gallstones 13 per cent, alcohol plus gallstones 2 per cent, trauma 1 per cent and idiopathic 12 per cent. A total of 26 of 81 patients (32 per cent) had greater than 50 per cent pancreatic necrosis and 9 patients (11 per cent) considered to have parenchymal necrosis at operation had none shown histologically. The overall mortality was 38/84 (45 per cent) and mortality during the first postoperative week was 15/84 (18 per cent). The outcome after early and delayed operation did not differ significantly. Pancreatic resection had no beneficial effect on shock or respiratory or renal failure (respective pre-operative incidence 12 per cent, 11 per cent and 14 per cent).

Keywords: Acute necrotizing pancreatitis, pancreatic resection, systemic complications

The poor prognosis in acute necrotizing pancreatitis is largely due to early systemic complications attributed to toxins released from the inflamed pancreas, or to late complications, which are mainly septic[1,2]. The role of pancreatic resection in the treatment of acute necrotizing pancreatitis is still controversial[3–5]. Early removal of inflamed pancreatic tissue should, theoretically, diminish the release of toxins into the circulation, thereby helping to prevent systemic multi-organ failure. Opinions vary concerning the optimal timing and extent of pancreatic resection[6–8].

The present study aimed to evaluate the immediate effects of pancreatic resection in acute necrotizing pancreatitis, and to compare the outcome of early and delayed operation.

Patients and methods

Eighty-four patients underwent pancreatic resection for acute necrotizing pancreatitis during a 12-year period beginning in 1973 The mean age of the 74 men and 10 women was 43·6 (range 19–70) years. The severity of pancreatitis was classified in accordance with Ranson's 11 prognostic signs, modified to suit our laboratory routines. The causes of the acute pancreatitis were alcoholism (60 cases), gallstones (11), alcohol abuse plus gallstones (2), trauma (1) or unknown (10).

The indication for laparotomy was clinically verified peritonitis or clinical deterioration despite intensive conservative treatment Contrast-enhanced CT was not used in our clinic during this study period The mean time from onset of symptoms to pancreatic resection was 5·6 days—less than 7 days in 68 patients and longer in 16. The groups did not differ significantly from each other (*Table 1*).

At the initial laparotomy, resection of inflamed pancreas was performed in 62 patients, but only drainage of patchy peripancreatic necrotic areas in 22 The latter patients underwent pancreatic resection after subsequent progression of parenchymal necrosis. The macroscopically evaluated extent of resection was to the left of the portal vein (3 cases), to the right of the portal vein (42 cases), to midway on the pancreatic head (26 cases), subtotal (12 cases) and pancreatoduodenectomy (1 case)

Histological evaluation of the extent of pancreatic parenchymal necrosis was possible in 81 of the 84 cases, with study of from 4 to 8 transverse sections from each specimen. Necrosis in resected parenchymal tissue was expressed on a scale from nil to 100 per cent

Evaluation of the patients pre-operatively and on postoperative days 2 and 7 included signs of shock (systolic blood pressure <80mmHg/15min), oliguria/anuria (output <1200ml/24h), renal failure (serum creatinine >230 μmol/l), arterial hypoxia (P_{O_2} < 60 mmHg), chest radiographic changes (pleural effusion, atelectasis, parenchymal infiltration) and acidosis (base deficit >4 mmol/l)

The χ^2 test was used for intergroup comparative analyses

Results

Of the 84 patients, 8 died within the first 2 postoperative days and 15 within the first week. The overall mortality was 45 per cent, ranging from 35 per cent to 100 per cent in the various resection groups (*Table 2*). The primary causes of the 38 deaths were multiple organ failure (9), complicating infection (19), bleeding into the gastrointestinal canal or abdominal cavity (4), myocardial infarction (1), pulmonary embolism (1) and miscellaneous (4). There was no statistical difference in mortality between the patients operated on within 7 days from the onset of symptoms and patients operated on later (*Table 1*)

Necrosis of peripancreatic and septal tissue was found at histological examination in all 81 studied cases, but no parenchymal necrosis in nine In 26 specimens there was more than 50 per cent necrosis (*Table 2*) which was more common in the group that underwent early operation (*Table 1*) Intra-operative bleeding was greatest when the resection extended to the head of the pancreas (*Table 2*).

Table 3 shows the results of arterial P_{O_2} and chest radiography. Pre-operatively there was atelectasis in 16 patients, pleural effusion in 15 and parenchymal infiltration in 5

Table 1 *Pre-operative clinical data, pancreatic necrosis and mortality in relation to time from onset of symptoms to operation*

	Interval to operation (days)	
	⩽7 (*n* = 68)	>7 (*n* = 16)
Mean age (years)	41·8	51·4
Number of Ranson signs (mean ± s d.)	4·4 ± 1·9	4·6 ± 2·0
Shock	9/68 (13%)	1/16 (6%)
Urinary output < 1200 ml/day	17/67 (25%)	3/16 (19%)
Serum creatinine > 230 μmol/l	9/65 (14%)	2/16 (13%)
Arterial P_{O_2} < 60 mmHg	7/66 (11%)	2/16 (13%)
Necrosis > 50%	23/67 (34%)	3/14 (21%)
Mortality	32/68 (47%)	6/16 (38%)

0007-1323/88/080793-03$3 00

Table 2 *Pancreatic necrosis, intra-operative blood loss and mortality in relation to extent of pancreatic resection*

	Pancreatic resection				
	Total ($n=1$)	Almost total ($n=12$)	Midway on pancreatic head ($n=26$)	To right of portal vein ($n=42$)	To left of portal vein ($n=3$)
Necrosis >50%	0	4/11 (36%)	10/26 (38%)	12/40 (30%)	0
Blood loss, ml (mean ± s.d.)	4050	5700 ± 4300	5900 ± 4050	4700 ± 3000	3000 ± 700
Deaths	1 (100%)	7 (58%)	9 (35%)	19 (45%)	2 (67%)

Table 3 *Arterial hypoxia and chest radiography changes before and after pancreatic resection*

		Postoperative day	
	Pre-operative	2	7
Arterial P_{O_2} < 60 mmHg	9/82 (11%)	14/77 (18%)	2/66 (3%)
Radiographic changes*	36/81 (44%)	54/73 (74%)	48/68 (71%)

* Atelectasis, pleural effusions, soft infiltrations

Table 4 *Signs of shock, renal insufficiency and acidosis before and after pancreatic resection*

		Postoperative day	
	Pre-operative	2	7
Shock	10/84 (12%)	9/80 (11%)	0
Serum creatinine >230 µmol/l	11/81 (14%)	15/76 (20%)	14/66 (21%)
Urinary output <1200 ml/day	20/83 (24%)	12/78 (15%)	8/67 (12%)
Base deficit >4 mmol/l	47/82 (57%)	12/76 (16%)	13/65 (20%)

Both hypoxia and intrathoracic changes were more frequent on the second postoperative day. Ventilatory support was required pre-operatively by one quarter of the patients for 1·7 ± 1·5 days and postoperatively by all but four patients for 14·7 ± 15·6 days.

Renal insufficiency was indicated pre-operatively by the serum creatinine values in 14 per cent and by the urinary output in 24 per cent of the patients. *Table 4* shows that the serum creatinine tended to rise postoperatively, though fewer survivors had low urinary output.

Changes reflecting pre-operatively severe hypoxia (arterial P_{O_2} < 60 mmHg) were found in 7 out of 9 patients (78 per cent), renal failure (serum-creatinine >230 µmol/l) in 9 out of 11 patients (82 per cent), vascular collapse in 9 out of 10 patients (90 per cent) and acidosis in 41 out of 47 patients (87 per cent) within 7 days from the onset of symptoms.

Discussion

Among the methods recommended for treating acute necrotizing pancreatitis are drainage alone, peritoneal lavage, debridement and pancreatic resection. The aims of surgery in these cases are to confirm the diagnosis, if possible correct causal factors, remove damaged pancreatic tissue and treat complications.

The timing (early or delayed) and the extent of pancreatic resection have been much debated. Criticism of early resection is based mainly on two assumptions: (1) that not all patients with severe early toxaemia benefit from such surgery[6,8], and (2) that early evaluation of pancreatic damage is difficult because the demarcation between vital and necrotic tissue is not established until the second week of the disease[1;7,9]. Accordingly, early operation may result in too radical excision at the expense of the exocrine and endocrine function of the pancreas. In the present series the necrotizing process was rapid, and extensive pancreatic necrosis was more commonly found at early than at delayed operation. The nine cases without parenchymal necrosis in the resected pancreas reflect the difficulty of accurate peroperative assessment of necrosis.

The heavier intra-operative bleeding in more extensive resections obviously could be ascribed to technical problems associated with the head of the inflamed pancreas. Mortality, on the other hand, did not differ significantly according to extent of pancreatic resection.

Vasoactive and toxic substances are released into peritoneal exudate and blood early in the course of pancreatitis, with adverse effects on remote organs[10,11]. Early death in acute necrotizing pancreatitis is often due to toxaemia and multi-organ failure, whereas the main causes of late death are septic complications. Beneficial effects of peritoneal lavage on early complications and mortality have been observed and attributed to removal of the pancreatic toxins from ascitic fluid[12–14], but contrary reports have also been published[15,16].

Some authors advocated early resection of the pancreas as producing an immediate favourable response[4,17]. Resection of the pancreas presumably reduces the release of toxins. In the present study, however, pancreatic resection had no immediate beneficial effect on the incidence of shock or pulmonary or renal insufficiency, which were found almost solely in the early phase of pancreatitis. Only acidosis was improved within the first two postoperative days, when 10 per cent of the patients had already died. On postoperative day 7 the survivors were improved in regard to shock, respiratory function and acidosis compared with the pre-operative state. The mortality was higher after early than after delayed surgery (47 *versus* 38 per cent), but the difference was not significant.

This study suggests that pancreatic resection does not offer benefit in the management of multi-organ failure due to acute necrotizing pancreatitis. Consequently we now avoid pancreatic resection in the early toxaemic phase of pancreatitis.

Acknowledgements

This study was supported by grant from the Reino Lahtikari Foundation.

References

1. Gebhardt C, Gall FP. Importance of peritoneal irrigation after surgical treatment of hemorrhagic, necrotizing pancreatitis *World J Surg* 1981; 5· 379–85
2. Knol JA, Eckhauser FE, Strodel WE. Surgical treatment of necrotizing pancreatitis by marsupialization. *Am Surg* 1984; 50· 324–8.
3. Alexandre J-H, Suerneri MT. Role of total pancreatectomy in the treatment of necrotising pancreatitis. *World J Surg* 1981; 5: 369–77.
4. Hollender LF, Meyer C, Marrie A *et al.* Role of surgery in the management of acute pancreatitis. *World J Surg* 1981, 5 361–8
5. Kivilaakso E, Lempinen M, Makelainen A *et al* Pancreatic resection versus peritoneal lavation for acute fulminant pancreatitis. *Ann Surg* 1984; 199: 426–31.
6. Aldridge MC, Ornstein M, Glazer G, Dudley HAF. Pancreatic

resection for severe acute pancreatitis. *Br J Surg* 1985; **72**: 796–800

7. Beger HG, Block S, Krautzberger W, Bittner R. Die nektonsierende Pankreatitis. *Chirurg* 1982, **53**: 784–9.
8. Smadja C, Bismuth H Pancreatic debridement in acute necrotizing pancreatitis. an obsolete procedure? *Br J Surg* 1986, **73** 408–10
9. Leger L, Chicke B, Louvel A. Pancreatic necrosis and acute pancreatitis. *World J Surg* 1981; **5**. 315–7.
10. Bradley EL, Hall JR, Lutz J *et al.* Hemodynamic consequences of severe pancreatitis. *Ann Surg* 1983; **198**: 130–3
11. Glazer G. Haemorrhagic and necrotizing pancreatitis *Br J Surg* 1975, **62**. 169–76.
12. Neher M, Schuster HP. Peritoneal lavage in severe pancreatitis. *Hepatogastroenterology* 1982, **29**: 263–4
13. Ranson JHC, Spencer FC. The role of peritoneal lavage in severe acute pancreatitis. *Ann Surg* 1978; **187**: 565–75
14. Stone HH, Fabian TC Peritoneal dialysis in the treatment of acute alcoholic pancreatitis *Surg Gynecol Obstet* 1980, **150**: 878–82.
15. Ihse I, Evander A, Gustafson I, Holmberg JT. Influence of peritoneal lavage on objective prognostic signs in acute pancreatitis *Ann Surg* 1986, **204**: 122–7.
16. Imrie CW. Peritoneal lavage in severe acute pancreatitis *Br J Surg* 1985; **72**. 677.
17. Kivilaakso E , Fraki O, Nikki P, Lempinen M Resection of the pancreas for acute fulminant pancreatitis *Surg Gynecol Obstet* 1981; **152** 493–8

Paper accepted 13 March 1988

Surgical workshop

Br. J. Surg. 1988, Vol. 75, August, 795

Primary anoplasty with skin flaps in posterior sagittal anorectoplasty

W. D. Ng, Y. T. Chan and H. Fung

Surgical 'B' Unit, Princess Margaret Hospital, Lai Chi Kok, Kowloon, Hong Kong
Correspondence to: Dr W D Ng

Anatomic reconstructive surgery for high imperforate anus has been a challenging exercise. Even now, there is still room for improvement. Posterior sagittal anorectoplasty represents a rational approach and is gaining popularity. The wide perineal exposure affords precise identification of the sphincter components and accurate placement of the bowel. However, recently, concern has been expressed about the possibility that the direct mucocutaneous anastomosis flush with perineal skin could result in distressing complications of stenosis and mucosal ectropion. We describe a modification incorporating primary anoplasty with local skin flaps. This produces superior functional and aesthetic results.

Method

With the baby in the prone jack-knife position, the distal bowel is exposed via a long midline incision after splitting successive muscle layers strictly sagittally. The bowel is opened longitudinally by a dorsal incision to reveal the opening of the recto-urethral fistula The mucosa around the opening is circumcised and the fistula closed, leaving a ventral slit in the terminal end of the bowel. The bowel is mobilized until it can be brought down to within 7·5 mm from the perineal skin level Partial suturing of the dorsal longitudinal incision with or without tapering of the bowel leaves a terminal 1 cm dorsal slit. The sphincter musculature is reconstituted as described by de Vries and Pena[1].

From the original wound edges, two skin incisions are then made (*Figure 1*), to allow elevation of two triangular skin flaps with the broad base lying on either side of the proposed anal site. When the lateral skin edge bordering the triangular donor defect is retracted medially by the skin hook, the skin flaps will undergo 180° rotation and interdigitate with the slits in the anterior and posterior wall of the rectum and, simultaneously, skin from both buttocks is drawn medially. For convenience, mucocutaneous anastomosis is performed before complete suture closure of the donor defects But once the latter is done, buttock skin on both sides of the donor defects is securely displaced medially, allowing further ascent of the mucocutaneous junction.

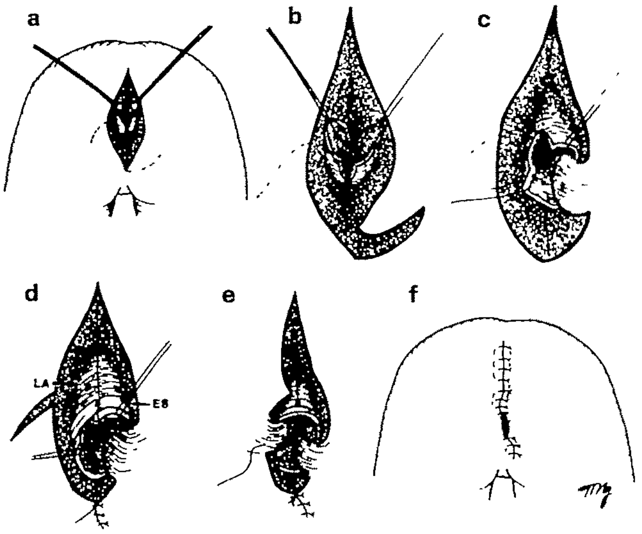


Figure 1 *Operative details.* **a** *Near the completion of Pena's operation, incisions for skin flap anoplasty are marked (dotted lines)* **b** *The anterior flap is elevated and is about to rotate 180° to be inserted into the ventral slit of the distal rectum* **c** *The comparatively big flap is stitched to the slit edge, as well as the adjacent cut end of the bowel* **d** *The donor defect is being closed longitudinally, pulling adjoining buttock skin medially The external sphincter layers (ES) and Levator muscle (LA) are conveniently repaired at this stage.* **e** *Similarly, the posterior flap rotates backwards and inwards to fit into the dorsal rectal wall slit.* **f** *The resulting donor defect is closed by approximating opposing skin edges, thereby further inverting the anal orifice*

Discussion

Apart from being technically simple, our modification carries several advantages The interdigitating suture line minimizes the chance of a stricture. A skin-lined anal canal, as in normal anatomy, is essential in preventing exposure of rectal mucosa with its attendant problems of irritation, wetting and bleeding. Its cutaneous sensation may contribute to faecal control and perineal cleanliness. The extent of mobilization of the bowel is lessened and accordingly the risk of haematoma and nerve damage is reduced as the maximum length of the bowel is utilized in our technique without extensive trimming and the bowel does not need to be fully drawn down to the skin level.

We believe that skin-flap anoplasty is an integral part of any operation for imperforate anus.

References

1. de Vries PA, Pena A Posterior sagittal anorectoplasty. *J Pediatr Surg* 1982; **17** 796–811

Paper accepted 26 February 1988

0007-1323/88/080795-01$3 00 © 1988 Butterworth & Co (Publishers) Ltd

Br. J. Surg. 1988, Vol. 75, August,
796–798

Gallbladder non-filling: an indication for cholecystectomy after endoscopic sphincterotomy

C. S. Worthley and
J. Toouli

Department of Surgery, Flinders University of South Australia, Bedford Park, South Australia, 5042
Correspondence to:
Dr C. S. Worthley, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia, 5042

The place of endoscopic sphincterotomy in the treatment of common duct stones leaving the gallbladder in situ *remains controversial. Over a 3-year period, 20 elderly high-operative-risk patients with stones in the common duct and intact biliary tree were treated by endoscopic sphincterotomy leaving the gallbladder* in situ. *Two patients underwent cholecystectomy for persistent symptoms after endoscopic sphincterotomy, and 18 patients were discharged from hospital, with the gallbladder intact. Of the 18 patients, 6 developed recurrent gallbladder problems, with 3 of the 6 dying as a result of these problems. On review of our data, these six patients were in a group of eight who, at the time of original endoscopic retrograde cholangiography (ERC), were shown to have an obstructed cystic duct. The other 10 patients, with a patent cystic duct and discharged with gallbladder* in situ, *remained symptom free over a median follow-up period of 9 (range 2–42) months. We conclude that if the gallbladder does not fill at ERC (indicating probable cystic duct obstruction), cholecystectomy is warranted. When the gallbladder fills, regular follow-up alone is justified in the absence of symptoms.*

Keywords: Cholelithiasis, common bile duct, calculi, endoscopy, gallbladder diseases, bile duct obstruction, extrahepatic

Endoscopic sphincterotomy in the management of common duct stones in patients with a gallbladder is reported increasingly in the literature, mainly in patients with poor anaesthetic risk but also in those with jaundice, cholangitis and gallstone pancreatitis[1–11]. The patients may proceed to early elective cholecystectomy or be discharged with their gallbladder *in situ*. Cystic duct obstruction has been suggested as a potential predictor of future biliary problems in asymptomatic patients with gallbladder stones[1,12,13].

The aim of this study was to assess outcome in patients of poor operative risk with common duct stones and a gallbladder *in situ* who were treated by endoscopic sphincterotomy alone. Furthermore, we analysed the significance of gallbladder non-filling at endoscopic retrograde cholangiography (ERC), a potential indicator of cystic duct obstruction, in predicting further gallbladder problems.

Patients and methods

Twenty patients, with an intact gallbladder, had endoscopic sphincterotomy for common duct stones between September 1983 and December 1986. Their median age was 80 (range 51–89) years with a M:F ratio of 3·2. All 20 patients had concurrent medical illnesses which increased the risks of abdominal surgery, hence they were referred for treatment of the common duct stones via the endoscopic method (*Table 1*). All patients had symptoms and signs of biliary stone disease; 90 per cent were jaundiced, 60 per cent had pain requiring parenteral analgesics, 10 per cent had pancreatitis and 40 per cent were febrile.

All patients received intravenously administered broad-spectrum antibiotics 1 h before endoscopy. After medication with pharyngeal local anaesthesia (atropine, diazepam and glucagon), ERC was performed using a standard duodenoscope The common bile duct was freely cannulated and 30 per cent Urografin* mixed in normal saline injected to opacify the biliary tree Multiple X-rays were taken and the patient positioned so as to maximize gallbladder filling. The cystic duct was considered obstructed if the gallbladder was not visualized after sufficient contrast was injected to opacify the extrahepatic ducts densely and to fill the tertiary intrahepatic branches.

Endoscopic sphincterotomy was performed with a Demling[14] papillotome using alternating coagulation and cutting diathermy The length of the sphincterotomy depended on the size of the common bile duct calculus, and in general was in excess of 1·5 cm. An assessment of length was made using the markings on the papillotome.

After sphincterotomy, the patients were fasted until the pharyngeal anaesthesia wore off and fluids and food were then introduced over the next 24 h, as tolerated Those patients who remained asymptomatic were discharged home. If symptoms persisted, these were treated according to the cause.

ERC was repeated in 17 of the 20 patients 6–12 weeks after sphincterotomy in order to assess common duct clearance. In three patients, follow-up ERC was not performed, the clinical status and biochemical investigation alone being used to decide outcome. All patients were examined 3 months after the procedure and then by personal and telephone interview. All patients with continuing symptoms were re-examined and investigated as warranted.

Comparisons with regard to outcome were made using the Fisher exact test[15] taking $P<0.05$ as significant Data are presented as the median plus range

Results

After endoscopic sphincterotomy, two patients with a patent cystic duct required cholecystectomy for continuing symptoms (*Table 2*). Six (33 per cent) of the remaining 18 patients who were discharged with gallbladder *in situ* developed gallbladder-related problems within a median follow-up period of 8 months. For further analysis, the patients were subdivided into two groups depending on whether or not there was gallbladder

Table 1 *Major concurrent medical illness*

Concurrent illness	Gallbladder filled ($n=12$)	No gallbladder filling ($n=8$)
Obstructive airways disease	2	3
Congestive cardiac failure	3	1
Cerebral vascular disease	1	1
Ischaemic heart disease	4	3
Parkinson's disease	1	—
Hypertension	1	—

---

* *Schering, Berlin, FRG*

0007–1323/88/080796–03$3.00

filling on ERC. There were no significant differences in the severity of symptoms or signs between the two groups and, in particular, no patient had clinical evidence of persistent acute cholecystitis. The results of treatment are summarized in *Table 2*. In 10 of the 18 patients the gallbladder had filled on ERC. Three of these patients did not have common duct stones at the time of sphincterotomy. However, in all three there had been recent evidence of passage of a stone (pancreatitis, 1; jaundice, 2). All three patients had small stones in the gallbladder and endoscopic sphincterotomy was performed. All 10 of these patients were discharged with gallbladder *in situ* and none has had subsequent biliary problems at a median follow-up of 9 months since sphincterotomy. Two patients remain asymptomatic despite the continuing presence of large stones in the common bile duct. Two other patients have died of non-biliary causes.

Six of eight patients without gallbladder filling at ERC required cholecystectomy (*Table 3*). Four of these eight patients have died and three of these deaths have been related to the gallbladder. One patient with moderately severe chronic obstructive airways disease developed acute cholecystitis which was managed conservatively in a remote hospital. He developed septic complications and died without further surgical or endoscopic treatment. A second patient, also with chronic obstructive airways disease, presented acutely with a ruptured gallbladder. This was treated surgically but he died postoperatively from septic complications A third patient developed a cholecystocholedochal fistula, associated with acute cholecystitis and cholangitis after a stone in the gallbladder eroded into the bile duct. Endoscopic and operative intervention restored normal biliary anatomy; however, continuing hepatobiliary sepsis resulted in her death from cardiac and renal causes. A fourth patient died of a myocardial infarction but had no biliary symptoms. Three other patients had uneventful cholecystectomies following acute cholecystitis (two patients) and cholangitis associated with sphincterotomy stenosis (one patient). An additional patient has recurrent biliary colic which may be due to continuing disease in the gallbladder. However, she also has a large stone in the common duct which has not been cleared despite a long sphincterotomy. Associated medical problems have precluded surgical intervention in this patient, her symptoms were treated conservatively.

Table 2 *Follow-up results after endoscopic sphincterotomy in patients with an intact gallbladder*

	Gallbladder filled ($n=12$)	No gallbladder filling ($n=8$)
Early cholecystectomy	2	0
Discharged, gallbladder *in situ*	10	8
Follow-up (months)*	9 (2–42)	7 (3–28)
Maximum CD stone diameter (mm)*	12 (0–24)	9 (3–20)
Residual CD stones	2	1
Cholecystectomy needed	0	6†
Gallbladder-related deaths	0	3

* Median and range, † $P<0\cdot01$, Fisher's exact test (gallbladder filled *versus* no gallbladder filling); CD, common duct

Discussion

This study has demonstrated that endoscopic sphincterotomy, leaving the gallbladder *in situ*, is associated with complications in 33 per cent (6/18) of patients within a median follow-up period of 8 months. Previous studies of this method of treatment report biliary complications in 0–22 per cent of patients over follow-up periods extending up to 7 years[2–11]. In a previous series of 22 patients[13] treated in this way, the authors concluded that an obstructed cystic duct may increase the chance of subsequent gallbladder problems. However, more recently in two other series[11,16] an association between non-filling of the gallbladder at ERC and subsequent gallbladder problems has not been found. In one study, 81 patients had endoscopic sphincterotomy with the gallbladder *in situ* and 17 patients required cholecystectomy for gallbladder problems The majority of the patients requiring cholecystectomy had a patent cystic duct as demonstrated by ERC, leading to the conclusion that an obstructed cystic duct does not influence subsequent outcome. However, contrary to our study and that of Solhaug *et al.*[13] no data are given on the outcome of patients with non-filling of the gallbladder at ERC. Furthermore, in this series, attempts at gallbladder filling were not made. Thus the findings and conclusions regarding obstructed cystic duct have not been addressed by these studies. In our series, all patients who developed gallbladder problems displayed non-filling of the gallbladder on ERC, whereas the patients who have remained well demonstrated a patent cystic duct. However, as noted in other series, two of our patients with a patent cystic duct continued to have gallbladder symptoms despite endoscopic sphincterotomy and they required cholecystectomy before discharge from hospital. The sign of non-filling of the gallbladder at ERC when the common duct has been freely cannulated and the intrahepatic ducts displayed indicates obstruction of the cystic duct[17,18]. The obstruction may be due to an impacted stone in Hartmann's pouch plus surrounding acute and chronic inflammation. Whether this obstruction persists after relief of the acute inflammation is not evident from our study. However, in the light of subsequent outcome in these patients we expect that the obstruction had persisted. Rohrmann *et al.*[19] studying a group of patients mainly with acalculous gallbladder disease showed that cystic duct obstruction on ERC did not correlate with obstruction of the cystic duct at operation or autopsy. However, the lack of correlation in this study may be owing to the absence of gallstones in the majority of their patients and this is not comparable with our series

In our study, if the gallbladder did not fill at ERC, six of eight patients required cholecystectomy within a median period of 7 months. Conversely, if the gallbladder filled and the patient's initial symptoms resolved following sphincterotomy, then all of the 10 patients with a patent cystic duct who were discharged

Table 3 *Indications for cholecystectomy after endoscopic sphincterotomy in patients with a non-filling gallbladder*

Patient	Age (years)	Sex	Indication	Time after ES (months)	Outcome
1	65	M	Acute cholecystitis	27	Death
2	73	M	Ruptured gallbladder	3	Death
3	85	F	Cholecystocholedochal fistula	3	Death
4	82	M	Acute cholecystitis	3	Cholecystectomy; normal recovery
5	73	M	Ampullary stenosis, cholangitis	3	Cholecystectomy, choledochoduodenostomy; normal recovery
6	64	M	Acute cholecystitis	27	Cholecystectomy; normal recovery

ES, endoscopic sphincterotomy

with the gallbladder *in situ* remained asymptomatic for a median follow-up period of 9 months. In a previous follow-up study[11] of patients with gallbladder stones and minimal symptoms, opacification of the gallbladder by oral cholecystography was assessed as a means of predicting future gallbladder complications. At a median follow-up period of 2 years the incidence of cholecystectomy for such complications was significantly greater in patients demonstrating non-opacification of the gallbladder when compared with patients in whom it opacified on oral cholecystography. Thus, both of these studies support the conclusion that cystic duct obstruction in the presence of stones in the gallbladder predicts future gallbladder complications.

A major source of concern in our study has been the severity of the gallbladder complications in those patients with an obstructed cystic duct having endoscopic sphincterotomy and leaving the gallbladder *in situ*. These complications have led to death in three patients, these deaths being attributable to overwhelming sepsis. Undoubtedly the age and general health of the patients also contributed to the outcome as these patients initially underwent endoscopic therapy because of the greater risks associated with abdominal surgery[20,21]. However, the presence of a sphincterotomy with the potential communication between the duodenum and a diseased gallbladder may have contributed to the severity of the complications[22].

The adequacy of the sphincterotomy, size and number of stones and clearance of the common duct are not significant variables in our series in that only one patient with a non-filling gallbladder had a large residual stone in the common duct after a long sphincterotomy, whereas two patients in the group with opacified gallbladder still have large stones in the common duct. None of these three patients has developed further gallbladder complications, although the former continues to have symptoms.

The findings of our study lead us to conclude that in medically compromised patients with common bile duct stones and an intact gallbladder, endoscopic sphincterotomy leaving the gallbladder *in situ* is justified if the gallbladder fills with contrast at ERC and the symptoms resolve following the procedure. However, early surgical review is needed for recurrent biliary symptoms. Should the gallbladder fail to opacify despite free cannulation of the common bile duct, dense opacification of the extrahepatic biliary tree and filling of the tertiary intrahepatic bile ducts, then cholecystectomy is recommended to avoid future gallbladder complications.

References

1. Cotton PB. Endoscopic management of bile duct stones, (apples and oranges). *Gut* 1984; **25**: 587–97.
2. Safrany L, Cotton PB. Endoscopic management of choledocholithiasis. *Surg Clin North Am* 1982; **62**: 825–36.
3. Escourrou J, Cordova JA, Lazorthes F, Frexinos J, Ribet A Early and late complications after endoscopic sphincterotomy for biliary lithiasis with and without gallbladder '*in-situ*'. *Gut* 1984; **25**: 598–602.
4. Neoptolemos JP, Carr-Locke DL, Fraser I, Fossard DP. The management of common bile duct calculi by endoscopic sphincterotomy in patients with gallbladders *in-situ*. *Br J Surg* 1984, **71**: 69–71.
5. Seifert E, Gail K, Weissmuller J. Langzeitresultate nach endoskopischer sphinkterotomie *Dtsch Med Wochenschr* 1982; **107**. 610–14
6. Cremer M, Toussaint J, Dunham F, Jeanmart J. Endoscopic sphincterotomy with gallbladder *in-situ* (Abstract) *Gastrointest Endosc* 1981, **27**: 141.
7 Siegel JH. Endoscopic papillotomy in the treatment of biliary tract disease: 258 procedures and results *Dig Dis Sci* 1981; **26**: 1057–63.
8 Roberts-Thomson IC Endoscopic sphincterotomy of the papilla of Vater· an analysis of 300 cases. *Aust NZ J Med* 1984, **14**: 611–17
9. Kawai K, Nakajima M Present status and complications of EST in Japan. *Endoscopy* 1983; **15**. 169–72.
10. Moss JG, Saunders JH, Wild SR. Endoscopic papillotomy for removal of common bile duct stones without cholecystectomy *J R Coll Surg Edinb* 1985, **30**: 112–14
11 Martin DF, Tweedle DEF Endoscopic management of common duct stones without cholecystectomy *Br J Surg* 1987; **74**: 209–11.
12. Watts JMcK, Bradley B, Whiting M. Studies on the outcome of untreated gallstone disease *Southeast Asian J Surg* 1984; **7**: 8–12.
13. Solhaug JH, Fokstuen O, Rosseland A, Rydberg B. Endoscopic papillotomy in patients with gallbladder in-situ. *Acta Chir Scand* 1984; **150**: 475–8.
14 Classen M, Demling L. Endoskopische sphinkterotomie der papilla Vateri und steinextraktion aus dem ductus choledochus. *Dtsch Med Wochenschr* 1974; **99**: 496–7
15. Siegel S. *Non-parametric Statistics for the Behavioural Sciences*. New York. McGraw-Hill, 1956: 96–104
16. Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gallbladder *in-situ* considered unfit for surgery. *Gut* 1987; **28**: A1371.
17. Cotton PB, Williams CB. *Practical Gastrointestinal Endoscopy*. Oxford: Blackwell Scientific, 1980: 68.
18. Cotton PB. Progress report. ERCP. *Gut* 1977, **18**: 316–41.
19. Rohrmann CA, Ansel HJ, Protell RC, Silverstein FE, Silvis SE, Vennes JA Significance of the non-opacified gallbladder in endoscopic retrograde cholangiography. *AJR* 1979; **132**: 191–5.
20. McSherry CK, Glenn F. The incidence and causes of death following surgery for non-malignant biliary tract disease. *Ann Surg* 1980; **191**· 271–5.
21 Glenn F, Hayes DM The age factor in the mortality rate of patients undergoing surgery of the biliary tract. *Surg Gynecol Obstet* 1955; **100**. 11–18.
22 Cohn MS, Schwartz S, Faloon WW, Adams JT. Effect of sphincteroplasty on gallbladder function and bile composition. *Ann Surg* 1979; **189**. 317–21.

Paper accepted 22 March 1988

Br. J. Surg. 1988, Vol. 75, August,
799–801

Choledochal cyst: a 33-year review

J. F. R. Robertson and
P. A. M. Raine

Royal Hospital for Sick Children,
Yorkhill, Glasgow, UK
Correspondence to:
Mr J F R Robertson, Professorial
Unit of Surgery, City Hospital,
Hucknall Road, Nottingham
NG5 1PB, UK

We present 13 patients who were seen at Glasgow hospitals over a 33-year period. Only five (38 per cent) were children. Of the eight adults, two had complications of the cyst at presentation, namely biliary cirrhosis and cholangiocarcinoma respectively. Another adult patient developed a carcinoma in the cyst 9 years after internal drainage. The incidence of malignant change in the series was therefore 15 per cent. Only five patients have remained well after surgery: three had complete excision and two internal drainage. Of the eight other patients, one had complete excision, five had internal drainage, one had partial excision and one had cholecystectomy and (years later) sphincterotomy. We believe that excision of the cyst is the treatment of choice.

Keyword: Choledochal cyst

Choledochal cysts are believed to be of congenital aetiology, with most cases presenting in childhood[1]. The majority of reported cases come from the Orient where the abnormality appears more common. This paper reports on 13 patients with choledochal cysts seen in the surgical units of adult and paediatric hospitals in Glasgow over a 33-year period.

Patients

During the period 1 January 1953 to 31 December 1985, 13 patients (11 female and 2 male) are known to have presented in Glasgow with choledochal cysts; these comprised 8 adults (i.e. patients older than 16 years) and 5 children There are five general hospitals as well as the Royal Hospital for Sick Children (RHSC) in Glasgow and the records of these hospitals were reviewed. Together the hospitals have a catchment population of one million, although they also receive secondary referrals from the West of Scotland region (population 2·7 million). Of the 13 patients, 1 adult and 1 child came from outside the primary catchment area of the Glasgow hospitals.

The clinical details of the patients are given in *Tables 1* and *2*. The presenting features in children were abdominal swelling (four patients) and/or jaundice (two patients) while in adults they were abdominal pain (five patients) and/or jaundice (five patients) Two patients, one child and one adult, had pre-operative serum amylase measurement: in both cases the levels were normal.

The earliest two paediatric cases were diagnosed at laparotomy. The three most recent cases were diagnosed pre-operatively by ultrasound. The diagnoses in adults were made by various means· oral cholecystogram (one patient); intravenous cholangiogram (four patients), percutaneous transhepatic cholangiogram (one patient), endoscopic cholangiopancreatography (one patient) and laparotomy (one patient).

Results

A variety of operations were performed. Details of the paediatric cases are shown in *Table 1*. The earliest child (1) had partial excision of the cyst, which subsequently recurred requiring further surgery on three occasions. Two children had complete excision of their cyst. The first of these (2) had excision and primary anastomosis of the bile duct which was disrupted on removing the T tube at postoperative day 10. At the resulting operation she had a choledochoduodenostomy. Three years later the patient was admitted with hepatosplenomegaly. Biliary cirrhosis was diagnosed and a barium swallow showed oesophageal varices. The patient had three episodes of haematemesis before she was lost to follow-up at 6 years of age when her parents emigrated. The second child (4) had complete excision of the cyst. Liver biopsy at that time showed fibrosis secondary to biliary obstruction. Postoperatively hepatomegaly persisted with mild elevation of the transaminases (aspartate aminotransferase 78 units/l and alanine aminotransferase 56 units/l) and, in view of the hepatic biopsy report, she was treated with steroids for 3 years during which time she was clinically asymptomatic. For the last 3 years, without medication, she has remained well: clinical examination and ultrasonography have been normal although no liver function tests have been carried out since the steroids were stopped.

A fourth child (3) had Caroli's disease which involved dilatation of both extra- and intrahepatic ducts. She underwent cholecystectomy and a Roux loop of jejunum was brought up to the cystic duct. Liver function tests 6 months after surgery were normal. Three years after surgery the general practitioner reported a transient episode of jaundice. Subsequent clinical examination and liver function tests were normal and ultrasound showed no evidence of biliary obstruction; the patient remains well. The fifth child (5) had choledochocystoduodenostomy. She has been followed for 3 years during which time she has developed episodes of ascending cholangitis with periportal fibrosis. She is currently asymptomatic as far as her choledochal cyst is concerned, although long-term antibiotic therapy has been started for recurrent urinary tract infection. At her latest review 3 years after surgery, liver function tests showed an aspartate aminotransferase level of 53 units/l, alanine aminotransferase of 37 units/l, total bilirubin of 7 μmol/l, total protein of 63 g/l and albumin of 42 g/l. The aspartate aminotransferase was minimally elevated but the other values are all within normal ranges.

Details of the adult cases are shown in *Table 2*. Two patients presented with complications of their cyst. In one patient, a cholangiocarcinoma in the cyst was excised but she subsequently developed liver metastases and died. The other patient (6) had Caroli's disease involving both intra- and extrahepatic ducts. He presented initially with jaundice and biliary cirrhosis. After secondary presentation with portal hypertension, endoscopic retrograde choledochopancreatography and sphincterotomy were performed but he died from massive gastrointestinal haemorrhage from the sphincterotomy site and from disseminated intravascular coagulation.

Of the remaining six adults, four underwent choledochocystoduodenostomy and two had complete excision of the cyst; the latter two patients remain clinically well although neither have yet had liver function tests measured after surgery. Only one of the four patients who underwent drainage remained well until he was lost to follow-up one year after surgery. Another patient 9 years after internal drainage developed a carcinoma in the cyst with liver metastases, from which she died.

Discussion

The classic description of the presentation of choledochal cysts with jaundice, abdominal pain and swelling is now known to apply to only a minority of patients[1–3]. However, the belief that

Table 1 *Choledochal cysts in five children*

Patient	Year presented	Age at presentation	Surgery	Follow-up	Results
1	1953	5 years	Partial excision of cyst	7 years	Recurrence: further surgery
2	1960	1 year	Excision of cyst; choledochoduodenostomy	5 years	Biliary cirrhosis; portal hypertension; oesophageal varices; variceal haemorrhage
3	1978	3 years	Cholecystectomy; Roux-en-Y to cystic duct	4 years	Well
4	1980	9 months	Excision of cyst; choledochoduodenostomy	6 years	Well
5	1984	1 month	Choledochocystoduodenostomy	3 years	Cholangitis; periportal fibrosis

Table 2 *Choledochal cysts in eight adults*

Patient	Year presented	Age at presentation	Complications of cyst at presentation	Surgery	Follow-up	Results
6	1965	29 years	Ascending cholangitis; cirrhosis	Cholecystectomy	14 years	
	1979	43 years	Portal hypertension; oesophageal varices	Sphincterotomy	Postoperative haemorrhage	Died
7	1971	65 years		Choledochocystoduodenostomy	1 5 years	Cholangitis, cirrhosis
8	1972	32 years		Choledochocystoduodenostomy	9 years	Carcinoma in cyst; died
9	1973	69 years		Excision of cyst	4 years	Well
10	1973	62 years		Choledochocystoduodenostomy	3 months	Abdominal pain
11	1976	17 years		Choledochocystoduodenostomy	1 year	Well
12	1983	29 years		Excision of cyst with hepaticojejunostomy Roux-en-Y	1 year	Well
13	1984	41 years	Cholangiocarcinoma	Excision of carcinoma with hepaticojejunostomy Roux-en-Y	2 months	Liver metastases; died

choledochal cyst presents mainly in childhood still persists[1,4]. As in our own series, paediatric cases are concentrated in paediatric surgical centres, whereas adult cases present disparately to various district general hospitals. Adult cases are thereby under-reported and reviews of the literature have probably over-estimated presentation in childhood. In series reporting both adult and paediatric cases, from 40 per cent to 60 per cent of patients presented as adults. In our own review this figure was 62 per cent.

None of the five children presented with complications of their choledochal cyst, although complications have been reported in other series[7]. Two of the eight adults presented with complications—one with cholangitis and biliary cirrhosis and the other with cholangiocarcinoma. A second patient died from cholangiocarcinoma 9 years after choledochocystoduodenostomy, giving a 15 per cent incidence of malignancy in our series. The incidence of carcinoma arising in the cyst is reported to be between 2·5 per cent[6] and 15 per cent[8]. In a literature review by Todani *et al.*[8] of 63 patients with a choledochal cyst and malignant change, 41 per cent had malignant change at the time of presentation; this change was not seen in patients presenting before late adolescence. The female:male ratio of carcinoma in the series was 2·5:1.

Surgery was carried out by 12 different surgeons and the variety of operations performed are shown in *Tables 1* and *2*. Only five patients remained well after surgery: three had complete excision of the cyst and two had internal drainage. Of the other eight patients with persisting symptoms, only one had complete excision. We concur with recent papers which suggest that excision of the cyst, where possible, is the treatment of choice both for adults and children. However, the management of patients with Caroli's disease, classified as Type IVA by Todani *et al.*[9] (extensive extra- and intrahepatic dilatation) is less clear. One of our two patients with Type IVA disease is alive and well after internal drainage, although the follow-up is only 3 years. The other patient developed cholangitis and its sequelae, from which he subsequently died. Todani *et al.* recommend excision of the dilated extrahepatic bile duct with hemi-hepatectomy if intrahepatic bile duct dilatation is present and confined to one lobe of the liver. Reconstruction with a hepaticojejunostomy Roux-en-Y is advocated.

The main problems of Caroli's disease, even after such radical surgery, are infection and recurrent gallstone formation. Recently Barker and Kallideen[10] have described the successful management of Type IVA disease in one patient using a permanent-access hepaticojejunostomy. However, once again the follow-up is short.

Much current interest centres on the aetiology of choledochal cyst formation. Babbitt initially proposed that it was associated with an abnormal junction of the common bile duct and pancreatic duct[11]. Further studies have looked for morphological abnormalities[12,13] and pathophysiological abnormalities as reflected by intra-operative pressure measurements[14] No pressure studies were carried out on any of the patients in our own series and the lack of data on the anatomical relationships prevent any useful comment on the aetiology of choledochal cyst formation from this retrospective study.

In this 33-year review of choledochal cysts in a large, relatively fixed population we have highlighted the fact that the majority of patients presented as adults to general surgeons. Twenty-five per cent of adults had a complication of the cyst at presentation and 15 per cent of patients developed malignancy. Excluding the two patients who presented with complications of their cysts, only five out of eleven (45 per cent) patients were reported as clinically well after surgery. Preoperative diagnosis is clearly preferable in that it allows adequate assessment and treatment before surgery. Neither of the two children diagnosed at laparotomy did well. The 13 patients were treated by 12 adult or paediatric surgeons, some without particular interest in hepatobiliary-pancreatic surgery, and none with extensive experience of choledochal cysts. These factors may be reflected in the number of different operations performed, and in particular by the low number of cyst resections carried out and the poor results obtained.

We suggest that excision of the cyst where possible is the treatment of choice. Where bypass is carried out but cyst excision is technically possible, subsequent referral to a tertiary centre would appear appropriate. Resection of cysts by experienced hepatobiliary-pancreatic surgeons would, we believe, reduce the range of morbidity from choledochal cysts reported in our series. Clinical, biochemical and, where indicated, radiological examinations, should be part of long-term follow-up in all patients and is of paramount importance in patients where the choledochal cyst has not been completely excised.

Acknowledgements

The authors are grateful to the consultants at all the teaching hospitals who have allowed their patients to be included in this series. Thanks are also due to Mrs Sue Kenny for help in the preparation of the manuscript.

References

1. Saing H, Tam PKH, Lee JMH, Pe-Nyum. Surgical management of choledochal cysts: a review of 60 cases. *J Pediatr Surg* 1985; **20**: 443–8.
2. Powell GS, Sawyers JL, Reynolds VH. Management of adult choledochal cysts. *Ann Surg* 1981, **193**: 666–76.
3. Tsardakas E, Robnett AH. Congenital cystic dilation of the common bile duct. *Arch Surg* 1955; **72**: 311–27.
4. Hadidi A. Type I and III choledochal cyst. *Am J Dis Child* 1983; **137**: 663–5.
5. Flanigan DP. Biliary cysts. *Ann Surg* 1975; **182**: 635–42.
6. Yamaguchi M. Congenital choledochal cyst. Analysis of 1,433 patients in the Japanese literature. *Am J Surg* 1980; **140**: 653–7.
7. Kim SH. Choledochal cyst: Survey by the Surgical Section of the American Academy of Paediatrics. *J Pediatr Surg* 1981; **16**: 402–7.
8. Todani T, Tabuchi K, Watanabe Y, Kobayashi T. Carcinoma arising in the wall of congenital bile duct cysts. *Cancer* 1979; **44**: 1134–41.
9. Todani T, Narushe M, Watanabe Y, Tabuchi K, Okajima K. Management of congenital choledochal cyst with intra-hepatic involvement. *Ann Surg* 1978; **187**: 272–80.
10. Barker EM, Kallideen JM. Caroli's disease: successful management using permanent-access hepaticojejunostomy. *Br J Surg* 1985; **72**: 641–43.
11. Babbitt DP. Congenital choledochal cyst: New etiological concept based on anomalous relationship of the common bile duct and pancreatic bulb. *Ann Radiol* 1969; **12**: 231–40.
12. Arima E, Akita H. Congenital biliary tract dilatation and anomalous junction of the pancreatico-biliary ductal system. *J Pediatr Surg* 1979; **14**: 9–15.
13. Jona JD, Babbitt DP, Starshak RJ *et al.* Anatomic observations and etiologic and surgical considerations in choledochal cyst. *J Pediatr Surg* 1979; **14**: 315–20
14. Iwai N, Tokiwa K, Tsuto T, Vanagihara J, Takahashi T. Biliary manometry in choledochal cyst with abnormal choledocho-pancreatico ductal junction. *J Pediatr Surg* 1986; **21**: 873–6.

Paper accepted 26 February 1988

Case report

Br. J. Surg. 1988, Vol. 75, August, 801–802

Ischaemic atrophy of the cervical portion of a substernal colic transplant: successful reconstruction using a synthetic resorbable tube

D. Gossot and J.-F. Lefebvre*

*Department of Surgery, Hôpital Saint-Louis, Paris, France and *Hôpital des Peupliers, Croix Rouge Française, Paris, France*

Correspondence to: Dr D. Gossot, Service de Chirurgie, Hôpital Saint-Louis, 1 Av. Cl. Vellefaux, 75010, Paris, France

Ischaemia and stenosis of the distal portion of a substernal colic transplant is not exceptional[1–3]. The main causes of ischaemia are torsion of the pedicle, or, more often, compression of the transplant by the sternal manubrium and the internal portion of the left clavicle[1,4]. We report one such case successfully reconstructed using a synthetic resorbable tube.

Case report

A 24-year-old man underwent a substernal colic interposition 3 months after an emergency oesophagogastrectomy for caustic burn of the upper digestive tract. The right ileocolon, vascularized by the right ileocolic artery, was used as the transplant. On the sixth postoperative day, a productive cervical fistula occurred, which closed spontaneously within 15 days. After closure of the fistula, the patient was unable to eat solid food. Contrast studies (*Figure 1*) showed indisputable ischaemic atrophy of the colic transplant[5]. Reoperation 3 months later showed complete destruction of the cervical part of the colic transplant; normal colic tissue was found just beneath the sternal manubrium. However, it was impossible to free the colon graft in order to pull it up to the neck. It was therefore decided to interpose a synthetic tube between the colic transplant and the remaining portion of the cervical oesophagus. A tube 5 cm long and 2 cm wide was made from polyglactin mixed with collagen*. This was interposed using resorbable interrupted 4/0 sutures for the anastomoses. Oral feeding was started on the eighth day. A small cervical fistula occurred on the tenth postoperative day; it closed spontaneously within 8 days. Because of recurrent dysphagia, endoscopic dilatation was performed 30 days after the second surgical procedure. At endoscopy it was impossible to differentiate between the synthetic tube and the normal colic transplant. Nine dilatation sessions

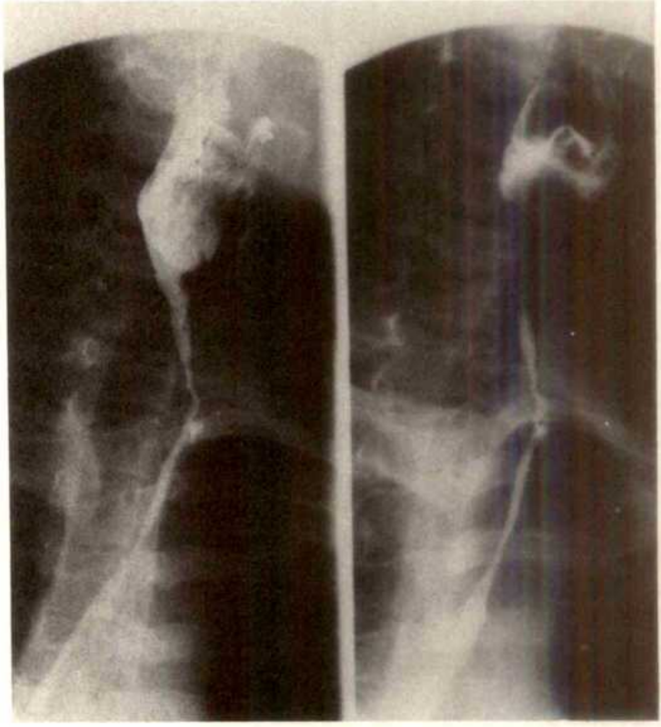


Figure 1 *Barium swallow 3 weeks after colon transplant, showing extensive ischaemic stenosis of the distal portion of the graft*

---

* *Collagen/Vicryl (Ethnor, France)*

0007–1323/88/080801–02$3.00

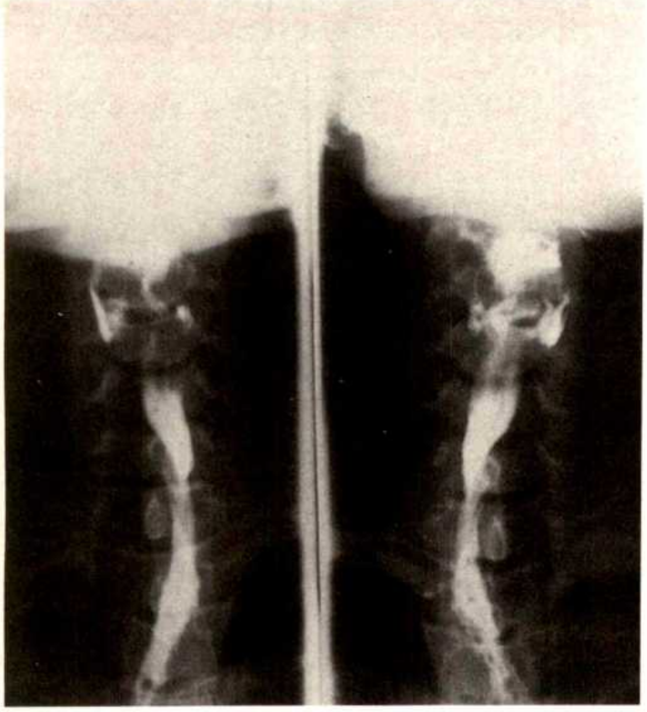


Figure 2 *Barium swallow 6 months after reconstruction using the synthetic resorbable tube*

were necessary to obtain a satisfactory and stable result (*Figure 2*). Nine months after reoperation, the patient was able to eat normally. His weight remained stable for the last 6 months without any enteral supplementation and he had resumed work.

Discussion

Several treatments are available for failure of a substernal colic transplant due to necrosis of its distal portion: interposition either of a muscular flap[6] or of a free jejunal graft[7] between the cervical oesophagus and the remaining colon transplant, or dissection of the coloplasty in order to pull it up to the neck via a sternotomy[1]. When the length of the transplant is not sufficient, a new colon transposition after removal of the transplant may be feasible[3]. All these procedures have a high mortality and morbidity, and do not always give good functional results. The procedure we have used in this case has two advantages: first, an exclusively cervical approach, avoiding postoperative mediastinal infection; secondly, the option to use another major procedure if the operation fails.

In our patient, the only postoperative complication was a fistula and a stenosis of the lower anastomosis, which required repeated dilatation. The replacement of oesophagus using a synthetic prosthesis has already been described[8,9]. However, the material used was non-resorbable, explaining the high failure rate, which was related to infection of the prosthesis[8]. The tube we used was made of a new resorbable material (polyglactin mixed with collagen). This material is perfectly water-tight, well tolerated and resorbable[10,11], thus limiting the dangers of a potential infection.

References

1. Kotsis L, Krisar Z, Imure J, Csikos M. Complications of oesophagoplasty with isoperistaltic transverse colon. *Scand J Thorac Cardiovasc Surg* 1983; **17**: 317–21.
2. Higton DIR, Lord IJ. Dysphagia following colon pedicle grafts. *Br J Surg* 1970; **57**: 825–8.
3. Tremolada C, Ruol A, Nosadini A, Rossi M, Perrachia A. Réinterventions pour fistule après anastomose oesophagienne. *Lyon Chir* 1986; **6**: 378–80.
4. Kirk RM. Partial and complete sternotomy for blunt oesophagectomy. *Br J Surg* 1987; **74**: 685–7.
5. Agha FP, Orringer MB. Colonic interposition: radiographic evaluation. *AJR* 1984; **142**: 703–8.
6. Doberneck RC, Orschwald DL, Orgel MG. Use of a tubed pectoralis major myocutaneous flap for salvage of a failed colonic bypass of the esophagus. *Surg Gynecol Obstet* 1986; **162**: 477–9.
7. Kasai M, Nishihira T. Reconstruction using pedicled jejunal segments after resection for carcinoma of the cervical esophagus. *Surg Gynecol Obstet* 1986; **163**: 145–52.
8. Schuring AG, Ray JW. Experimental use of dacron as an esophageal prosthesis. *Ann Otol Rhinol Laryngol* 1966; **75**: 202–7.
9. Battersby JS, King H. Esophageal replacement with plastic tubes. *Arch Surg* 1954; **69**: 400–5.
10. Monsour MJ, Mohammed R, Gorham SD, French DA, Scott R. An assessment of a Collagene/Vicryl composite membrane to repair defects of the urinary bladder in rabbits. *Urol Res* 1987; **15**: 235–8.
11. Gossot D, Celerier M, Sarfati E. Protection des anastomoses cervicales après coloplastie retrosternale par un treillis résorbable imprégné de colagène. *Presse Méd* 1988; **17**: 30–2.

Paper accepted 29 March 1988

Br. J. Surg. 1988, Vol. 75, August, 803–806

Benign disease of the common bile duct

The incidence of common bile duct (CBD) pathology in a group of patients with benign biliary disease (n = 505) *was found to be 23·2 per cent. The spectrum included 111 patients (90·2 per cent) with CBD stones, 37 of whom (33·3 per cent) had no symptoms or findings pre-operatively indicating CBD involvement. Five patients had papillary stenosis, three had postoperative CBD strictures, one had a choledochal cyst and one had an external biliary fistula. Of the 100 CBDs measuring more than 10 mm in diameter, 90 harboured calculi. In the remaining 23 CBDs measuring less than 10 mm, calculi were present in 21. The presence of CBD calculi was demonstrated by intra-operative cholangiography in 49 patients. In the remaining patients* (n = 74)*, the diagnosis of CBD pathology was made either by percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography, T-tube cholangiography or peroperative palpation. The surgical procedures performed included choledochotomy and T-tube drainage* (n = 74)*, transduodenal sphincteroplasty* (n = 27) *and choledochoduodenostomy* (n = 18)*. The overall mortality and morbidity of CBD exploration was 3·3 per cent and 24·4 per cent respectively, which was significantly greater than that for cholecystectomy alone (0·3 per cent and 8·6 per cent respectively). Transduodenal sphincteroplasty carried a much higher mortality (11 per cent) and morbidity (52 per cent) when compared with other procedures.*

Keywords: Common bile duct, choledocholithiasis, intra-operative cholangiography, transduodenal sphincteroplasty, choledochoduodenostomy

R. Saxena, R. Pradeep, J. Chander, P. Kumar, J. D. Wig, R. V. S. Yadav and S. P. Kaushik

Department of Surgery,
Postgraduate Institute of Medical Education and Research,
Chandigarh—160 012, India

Correspondence to:
Dr S. P. Kaushik

The reported incidence of choledocholithiasis in patients undergoing cholecystectomy for stone disease has varied from 8 to 18 per cent[1–3]. The mortality and morbidity of common bile duct (CBD) exploration has been found to vary from 0·6 to 6·7 per cent and from 9·1 to 18·9 per cent respectively. These figures are significantly higher than those for simple cholecystectomy with its 0·2–1·2 per cent mortality rate and 5·1–9·4 per cent morbidity rate[4–11].

The present study was undertaken to assess the occurrence and nature of benign disease of the common bile duct in one Indian surgical centre and to determine the influence of CBD exploration on mortality and morbidity.

Patients and methods

At the Nehru hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh, India, 505 patients with benign biliary disease were operated upon in a single surgical unit between May 1980 and April 1987, and form the basis of this study. Benign biliary disease accounted for 15 per cent of admissions to the unit. A total of 123 patients underwent CBD exploration—21 males and 102 females; 111 of these patients (90·2 per cent) had choledocholithiasis, 5 had papillary stenosis, 3 had postoperative CBD strictures, 1 patient had a choledochal cyst, 1 had a choledochoduodenal fistula and yet another had an external biliary fistula following cholecystectomy. One patient with a normal CBD underwent a preliminary choledochotomy because of altered anatomy. Of the 382 patients who underwent cholecystectomy alone, 61 were males and 321 females. The average age of the male patients undergoing cholecystectomy alone was 43·1 years and of those undergoing CBD exploration was 53·1 years, the average ages for the corresponding female groups were 41·4 years and 43·8 years respectively. These differences were not statistically significant (Student's *t* test). All other statistical comparisons in this study were done with the χ^2 test.

Symptomatology

All of the 123 patients who underwent CBD exploration presented with recurrent episodes of right upper quadrant abdominal pain with or without vomiting, flatulence or fatty dyspepsia. Forty-nine patients were jaundiced on admission and of these, fourteen also had features of suppurative cholangitis, namely fever with chills and rigors and toxaemia. A past history of jaundice was present in 24, of acute pancreatitis in 9 and of previous biliary surgery in 13 patients.

One hundred and eleven patients (90·2 per cent) had stones in their CBD. Thirty-seven of these patients (33·3 per cent) had no symptoms pertaining to the CBD pathology in that they denied any history of biliary colic, jaundice or fever with chills and rigors, and there was no evidence to suggest biliary pancreatitis at any time during their illness.

Associated diseases

Thirty-three patients (26·8 per cent) had associated medical disorders in the form of diabetes mellitus ($n = 8$), hypertension ($n = 7$), ischaemic heart disease ($n = 4$), chronic obstructive pulmonary disease ($n = 4$), chronic pancreatitis ($n = 2$), cirrhosis of the liver ($n = 2$), portal hypertension ($n = 2$), pregnancy ($n = 2$), malnutration ($n = 2$) and severe anaemia ($n = 1$).

Diagnosis of CBD pathology and indications for exploration

A diagnosis of CBD pathology was made pre-operatively in 64 patients (52·0 per cent), peroperatively in 58 patients (47·2 per cent) and 1 patient underwent a preliminary choledochotomy because of altered anatomy. Pre-operative diagnosis was based on clinical history and findings on examination, biochemical abnormalities (raised serum bilirubin and/or serum alkaline phosphatase) and CBD imaging. Apart from oral cholecystography, which was performed in all non-jaundiced patients ($n = 73$), the other imaging modalities used were percutaneous transhepatic cholangiography ($n = 35$), endoscopic retrograde cholangiopancreatography ($n = 15$), ultrasonography ($n = 14$), cholecystocholangiography through a previous cholecystostomy tube ($n = 2$), T-tube cholangiography ($n = 5$), intra-operative cholangiography ($n = 49$), and CT scanning ($n = 1$). The use of different imaging modalities depended on their availability at the time of presentation. The results of the various modalities used for diagnosing CBD pathology are shown in *Table 1*.

A peroperative diagnosis of CBD pathology was established in 58 patients (47·2 per cent). This was based on an intra-operative

0007–1323/88/080803–04$3 00

Table 1 *Diagnostic imaging techniques used in patients undergoing common bile duct exploration*

Investigation	No. of patients	Result	Operative findings
Percutaneous transhepatic cholangiography	35	3 strictures 31 stones 1 choledochal cyst	Bismuth Type II strictures (3) 20 multiple calculi, 11 single Choledochal cyst (Type I)
Endoscopic retrograde cholangiopancreatography	15	2 papillary stenosis with stones 1 cystic duct stump blow-out 12 CBD calculi	All findings confirmed
Ultrasonography	14	10 CBD stones 4 dilated intrahepatic radicles only	All 14 had calculi (6 single and 8 multiple)
T-tube cholangiography	5	3 residual calculi (multiple in 1) 2 normal studies	All confirmed
Cholecystocholangiography	2	1 CBD calculus 1 CBD not seen due to obstructed cystic duct	Both CBDs contained stones, cystic duct obstruction because of an impacted stone
CT scanning	1	Gallstones and CBD calculi	Confirmed, multiple CBD stones
Intra-operative cholangiography	49	49 CBD calculi	44 CBD stones, 5 false positive

(A total of 237 intra-operative cholangiograms were performed in 505 patients undergoing surgery for benign biliary disease.)

CBD, common bile duct

cholangiogram alone in 31 cases (25·2 per cent). Palpation of the duct alone was responsible for demonstrating the pathology in nine cases (7·3 per cent) while the two were diagnostic in combination in 18 cases (14·6 per cent).

Operative findings

The CBDs of 117 patients were explored for choledocholithiasis either at the time of cholecystectomy or where cholecystectomy had been performed at an earlier date (the latter comprised eight cases, including three of residual calculi following previous choledochotomy and 4 retained stones with no previous choledochotomy). Stones were recovered from 111 of the 117 common ducts (94·9 per cent).

The stones were single in 46 patients (41·4 per cent), including 2 who had retained calculi. Eleven of these patients were asymptomatic as far as their choledocholithiasis was concerned. In the remaining 65 patients (58·6 per cent), two or more calculi were recovered from their CBDs. Twenty-six patients (40 per cent) in this sub-group were again asymptomatic for choledocholithiasis. Three patients with symptomatic multiple CBD calculi had associated intrahepatic calculi as well. The CBD was more than 10 mm in diameter in 61 patients (55·0 per cent), more than 20 mm in 29 patients (26·1 per cent), and within the normal range in 21 patients (18·9 per cent) with CBD stones.

Six of the 117 explorations were negative for stones, all had dilated ducts. Intra-operative cholangiography in five patients suggested the presence of stones but none were found. Two of these patients were considered to have papillary stenosis. The sixth patient underwent exploration because of a 'palpable' stone, the presence of which could not be confirmed by intra-operative cholangiogram due to failure to cannulate a very narrow cystic duct. On exploration, no stone was found and the papilla was normal on calibration. Postoperative T-tube cholangiograms in all of these six patients were normal.

Papillary stenosis was suspected if there was hold-up of dye at the lower end of the CBD on intra-operative cholangiography, in the absence of an impacted stone. On exploration of the duct and calibration of the lower end, failure to pass a 3 mm bougie through the papilla was taken as confirmatory evidence of stenosis. Papillary stenosis was present in 5 of the 117 (4·3 per cent) cases. The CBD in two of these patients was grossly dilated but contained no stones. In the other three, in addition, a single mobile stone was present.

Three patients were explored for post-cholecystectomy CBD strictures. All were Bismuth type II strictures with a <2 cm stump from the confluence of the ducts; one of these patients had a stone above the stricture.

The only patient with a choledochal cyst had a fusiform dilatation of the entire CBD with no involvement of the intrahepatic radicles. The gallbladder in this patient was hugely dilated but harboured no stones or sludge.

One patient with a CBD stone had a choledochoduodenal fistula together with a single faceted stone in the CBD; the gallbladder was shrunken and did not contain any stones and none were palpable in the intestine.

Table 2 *Nature and frequency of common bile duct pathology*

Pathology	No. of patients	Percentage
Dilated CBD (>10 mm)	100	81·3
Stones (with no other pathology)	86	69·9
Without stones	5	4·1
Papillary stenosis		
Without stones	2	1·6
With stones	3	2·4
CBD strictures (post-cholecystectomy)		
Without stones	2	1·6
With stones	1	0·8
Choledochal cyst	1	0·8
Normal-size CBD (≤10 mm)	23	18·7
Stones	21	17·1
Choledochoduodenal fistula	1	0·8
External biliary fistula (post-cholecystectomy)	1	0·8

CBD, common bile duct

Table 3 *Surgical procedures performed on the common bile duct in 123 patients*

Procedure	No. of patients	Percentage
CBD exploration with		
T-tube drainage	74	60·2
Transduodenal sphincteroplasty	27	21·9
Choledochoduodenostomy	18	14·6
Roux-en-Y hepaticojejunostomy	3	2·4
Cholecystectomy and Roux-en-Y choledochocystojejunostomy	1	0·8

CBD, common bile duct

The patient with post-cholecystectomy external biliary fistula had a cystic duct stump blow-out with frank bile peritonitis. There was no demonstrable CBD pathology.

One patient had grossly distorted anatomy in Calot's triangle with severe inflammation; the CBD was explored as a preliminary step in this patient and a prophylactic choledochostomy was carried out to facilitate dissection and identification of anatomy.

The CBD pathology found in the 123 patients is shown in *Table 2*.

Operative procedures

Concomitant cholecystectomy was performed in 115 patients (93·5 per cent). Thirteen patients (10·6 per cent) had had previous biliary surgery. The various surgical procedures performed are detailed in *Table 3*.

All patients with strictures underwent Roux-en-Y hepaticojejunostomy. The patient with a choledochal cyst underwent cholecystectomy and Roux-en-Y choledochocystojejunostomy. The patient with an external biliary fistula underwent exploration, ligation of the cystic duct stump and T-tube drainage of the CBD with peritoneal lavage and drainage. Sphincteroplasty was performed in 27 cases (21·9 per cent) where one or more of the following indications for CBD drainage were present: an impacted stone at the lower end of the CBD, multiple stones in the CBD or the presence of biliary sludge, intrahepatic calculi or papillary stenosis

Choledochoduodenostomy as a drainage procedure was performed in 18 cases (14·6 per cent). This was performed in ducts measuring more than 15 mm in diameter in the presence of multiple ductal or intrahepatic calculi or sludge.

Results

Postoperative mortality and morbidity

The mortality and the morbidity encountered are shown in *Tables 4–6*. No mortality or morbidity was observed in any of the patients undergoing hepaticojejunostomy. The patient who underwent exploration for external biliary fistula made an uneventful recovery.

In the group of patients undergoing CBD exploration and T-tube drainage ($n=74$) the morbidity rate was 20 per cent and one patient died. She was a 65-year-old woman who presented with deep jaundice and suppurative cholangitis, malnutrition, severe anaemia and chronic obstructive pulmonary disease. She had undergone cholecystectomy, choledocholithotomy and T-tube drainage. In the postoperative period she developed wound infection, burst abdomen, bile leak, bronchopneumonia, septicaemia and the adult respiratory distress syndrome, and expired on the 23rd postoperative day. In this group, one patient of the seven who underwent simple choledochotomy (without stone retrieval) and T-tube drainage had a transient bile leak; this settled spontaneously in three days.

Table 4 *Postoperative mortality*

Group	Total no. of patients	Mortality (n)	Percentage
CBD exploration (overall)	123	4	3·3
CBD exploration with			
T-tube drainage	74	1	1
Sphincteroplasty	27	3	11
Choledochoduodenostomy	18	0	—
Cholecystectomy alone	382	1	0·3

CBD, common bile duct

Table 5 *Postoperative morbidity*

Group	Total no. of patients	Morbidity (n)	Percentage
CBD exploration (overall)	123	30	24·4
CBD exploration with			
T-tube drainage	74	15	20
Sphincteroplasty	27	14	52
Choledochoduodenostomy	18	1	5
Cholecystectomy alone	382	33	8·6

CBD, common bile duct

In the group of patients undergoing CBD exploration and transduodenal sphincteroplasty ($n=27$), 14 patients developed a total of 10 complications with three resultant fatalities (11 per cent). All three were more than 50 years of age. Two of them (one with diabetes mellitus and jaundice and the other with cirrhosis of the liver and jaundice) developed postoperative pancreatitis and acute renal failure. The third patient, who presented with suppurative cholangitis and a history of previous myocardial infarction, had an impacted stone at the lower end of the CBD. In the postoperative period he developed a bile leak, wound infection, burst abdomen, resistant Gram-negative septicaemia, upper gastrointestinal bleeding and acute renal failure.

In the group of patients undergoing CBD exploration and choledochoduodenostomy ($n=18$), only 'one complication occurred. This patient had fever on the first two postoperative days, the cause of which eluded all investigations. There was no mortality in this group.

The overall mortality of CBD surgery in the series was therefore 3·3 per cent ($n=4$) and the morbidity was 24·4 per cent ($n=30$). The corresponding figures for cholecystectomy alone in the same period were 0·3 per cent and 8·6 per cent respectively. The mortality and morbidity of CBD exploration were significantly higher than those for cholecystectomy alone (respective values $P<0{\cdot}01$ and $P<0{\cdot}001$). The mortality associated with sphincteroplasty was significantly greater than that of T-tube drainage alone ($P<0{\cdot}05$). The morbidity associated with sphincteroplasty was also significantly greater than that of T-tube drainage alone ($P<0{\cdot}01$) and choledochoduodenostomy ($P<0{\cdot}01$).

Discussion

The routine use of intra-operative cholangiography has been widely recommended[12–14], but a selective use of intra-operative cholangiography in CBD evaluation has also been advocated[15]. In this series of 505 patients undergoing surgery for benign biliary disease, intra-operative cholangiography was performed in 237 cases with only 5 instances of negative exploration

Table 6 *Postoperative morbidity (observed complications and their incidence)*

Complication	CBD exploration and T-tube drainage ($n=15/74$)	CBD exploration and sphincteroplasty ($n=14/27$)	CBD exploration and choledochoduodenostomy ($n=1/18$)	Total ($n=30/123$)
Fever	7	10	1	18
Wound infection	6	5	—	11
Burst abdomen	3	1	—	4
Bile leak	4	5	—	9
Renal failure	3	3	—	6
Pancreatitis	—	2	—	2
Septicaemia	2	1	—	3
Intra-abdominal collection	2	1	—	3
Residual calculus	1	—	—	1
Bronchopneumonia	1	—	—	1
Basal atelectasis	3	—	—	3
Adult respiratory distress syndrome	1	—	—	1
Upper GI bleed	1	1	—	2
Haemobilia	1	—	—	1
Duodenal obstruction	—	1	—	1
Disseminated intravascular coagulopathy	1	—	—	1

CBD, common bile duct; GI, gastrointestinal following false positive identifications of stones (2·1 per cent). None of the patients with normal operative cholangiograms have so far presented with symptoms or signs of a retained CBD stone and hence we presume that there were no false negative results. Fifty-nine unnecessary choledochotomies, which might have been indicated on the grounds of clinical suspicion and biochemical pointers of choledocholithiasis, were prevented when an intra-operative cholangiogram demonstrated a normal ductal system. This experience is similar to that of Jolly *et al.*[13] and Cranley and Logan[14] who have highlighted the value of intra-operative cholangiography in reducing the incidence of negative choledochotomy and also in demonstrating otherwise unsuspected CBD calculi.

Thirty-seven patients (33·3 per cent) with choledocholithiasis in this series had no complaints referrable to their CBD pathology and did not manifest any biochemical abnormalities which suggested choledocholithiasis. In 31 of these patients, the pathology was detected by intra-operative cholangiography alone and palpation was useful in the remaining 6. Devlin *et al.*[12] have also observed that 38·7 per cent of their patients with stones in the ductal system had no indication whatsoever of their presence pre-operatively and were detected only at the time of intra-operative cholangiography.

In the total of 123 patients undergoing CBD surgery, the ductal diameter was more than 10 mm in 100 patients; 90 of these harboured one or more calculi. The ductal diameter was less than 10 mm in 23 patients; 21 of these had one or more stones. In the absence of an intra-operative cholangiogram, therefore, impalpable calculi in normal-sized ducts would have escaped attention.

With regard to drainage procedures, the mortality associated with choledochoduodenostomy in collected series has been reported as 1·8 per cent[16], although it has varied from 0 to 8 per cent with a morbidity of less than 5 per cent. In contrast, the mortality associated with sphincteroplasty has been found to be 5–10 per cent[16]. The respective figures for the mortality and morbidity of choledochoduodenostomy and sphincteroplasty in the present series were zero and 5 per cent, and 11·1 per cent and 51·8 per cent. Significant differences have also been observed in the morbidity rates of the two groups. However, a large percentage of patients (60·2 per cent in this series) fortunately do not require a drainage procedure after choledochotomy. The overall mortality and morbidity rates of surgery on the CBD were significantly higher when compared with those of cholecystectomy alone in our series. Similar experience has been reported in the literature[4–11].

The presence of associated medical diseases has a considerable influence on the postoperative mortality and morbidity. All four patients who died in this series had deep jaundice and two of them had suppurative cholangitis as well. Diabetes mellitus, cirrhosis of the liver and ischaemic heart disease were the associated medical diseases in three patients, while the fourth had severe chronic obstructive pulmonary disease and malnutrition. All four patients were over 50 years of age. Postoperative pancreatitis was always fatal while acute renal failure carried a mortality of 50 per cent (3/6 patients). McSherry and Glenn[17], in their analysis of the incidence and causes of death following surgery for non-malignant diseases of the biliary tract, concluded that advanced age (> 50 years), acute cholecystitis and CBD stones were the principal determinants of operative mortality. Cardiovascular disease (especially myocardial infarction) and liver disease (especially cirrhosis) were also major factors in operative mortality. In our experience, jaundice was a constant factor in all four deaths and cholangitis was complicated in two of them, together with other intercurrent medical diseases.

In conclusion, 23·2 per cent of patients undergoing surgery for benign biliary disease required surgery on the common bile duct. A significant proportion of CBD pathology may easily be missed unless intra-operative cholangiography is performed at the time of cholecystectomy. Although it is important not to miss and to eradicate CBD pathology, at the same time it is equally important to avoid unnecessary CBD exploration based on clinical and biochemical grounds alone. There is a significant increase in the mortality and morbidity following surgery on the CBD, especially if it is associated with sphincteroplasty as a drainage procedure. Choledochoduodenostomy is the preferred drainage procedure, particularly in patients having a ductal diameter of more than 15 mm, because of its very low morbidity and virtually no mortality, in contast to transduodenal sphincteroplasty.

References

1. Hampson LG, Petrie EA. The problem of stones in the common bile duct with particular reference to retained stones *Can J Surg* 1984; **7**: 361.
2. Colcock BP, Liddle HV. Common bile duct stones. *N Engl J Med* 1958; **258**: 264–6.
3. Martin JK Jr, Van Heerden JA. Surgery of the liver, biliary tract and pancreas *Mayo Clin Proc* 1980; **55**: 333
4. Bartlett MB, Waddell WR Indications for common duct exploration. *N Engl J Med* 1958; **258**: 164–7.
5. Colcock BP, Perey B. Exploration of the common bile duct *Surg Gynecol Obstet* 1964; **118**: 20–4.
6. Larson RE, Hodgson JR, Priestly JT The early and long-term results of 500 consecutive explorations of the common duct. *Surg Gynecol Obstet* 1966, **122**: 744–50
7. Glenn F, McSherry CK, Dineen P. Morbidity of surgical treatment for non-malignant biliary tract disease. *Surg Gynecol Obstet* 1968; **126**: 15–26.
8. Meyer KA, Capos NJ, Mittlepunkt AI. Personal experiences with 1,261 cases of acute and chronic cholecystitis and cholelithiasis. *Surgery* 1967, **61**. 661–8
9. Holm JC, Edmunds LH, Baker JW. Life-threatening complications after operations upon the biliary tract. *Surg Gynecol Obstet* 1968; **127**: 241–52
10. Boquist L, Bergdahl L, Andersson A Mortality following gall bladder surgery: a study of 3,257 cholecystectomies. *Surgery* 1972; **71**. 616–24.
11. Briele HA, Long WB, Parks LC Gall bladder disease and cholecystectomy: experience with 1,500 patients managed in a community hospital. *Am Surg* 1969; **35**: 218–22.
12. Devlin HB, Sahay AK, Tiwari PN *et al.* Cholecystectomy and a simple technique of operative cholangiography. *Br J Surg* 1978; **65**. 848–51.
13. Jolly PC, Baker JW *et al.* Operative cholangiography—a case for its routine use. *Ann Surg* 1968; **168**: 551–65.
14. Cranley B, Logan H. Exploration of the common bile duct—the relevance of the clinical picture and the importance of peroperative cholangiography. *Br J Surg* 1980, **67**: 869–72.
15. Thourston OG. Non-routine operative cholangiography. *Arch Surg* 1974; **108**: 512–15.
16. Gliedman ML, Gold MS. Choledochoduodenostomy. In: Schwartz SI, Ellis H, eds. *Maingot's Abdominal Operations*, 8th edn. Norfolk, Connecticut: Appleton-Century-Crofts, 1985: 1915–23
17. McSherry CK, Glenn F. The incidence and causes of death following surgery for non-malignant disease of the biliary tract. *Ann Surg* 1980; **191**: 271–5.

Paper accepted 26 February 1988

Br. J. Surg. 1988, Vol. 75, August, 807–810

Standardization of the surgical technique in breast-conserving treatment of mammary cancer

K. Aspegren, L. Holmberg* and H.-O. Adami*

Department of Surgery, Malmö General Hospital, Malmo and
**Department of Surgery, University Hospital, Uppsala, Sweden*
Correspondence to.
Dr L. Holmberg, Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden

A number of designations—for example excision, wide excision, lumpectomy, tylectomy, extended tylectomy, partial mastectomy, tumorectomy, segmental resection and quadrantectomy—have been applied to operative procedures aimed at treating mammary carcinoma with preservation of the breast. None of them, however, has been explicitly linked to a defined surgical technique and there is no consensus about the terminology. We propose a simple classification system for breast-conserving procedures, which can facilitate the communication between surgeons and the interpretation and exchange of scientific data. We also describe a strictly defined and locally radical partial mastectomy—a sector resection—which has been used at several centres in Sweden for more than 5 years with a favourable outcome so far in terms of local tumour control and the cosmetic result.

Keywords: Breast cancer, breast conserving treatment, surgical technique

Breast-conserving surgical procedures have become established as a definite therapeutic option in certain cases of female breast cancer[1]. Although supported by the results of a large number of uncontrolled studies[2], this development is based mainly on randomized clinical trials[3–6] which have shown that the survival and local tumour control after breast preservation are comparable to those achieved with more radical procedures, including mastectomy. Further development of breast-conserving treatment of mammary cancer and reporting of the results is hampered, however, by the vague and widely differing descriptions of the surgical technique.

In this report we give a detailed description of a sector resection which has been used routinely for more than 5 years in several Swedish centres. This procedure, which can be strictly standardized, probably provides optimal possibilities for local tumour control with preservation of the breast. We also propose a classification of breast-conserving procedures which can facilitate the communication between surgeons in this field, standardization in clinical trials, and comparison between different patient populations.

Completed trials

Conservative treatment has been compared with mastectomy in only four randomized trials. Local surgery was followed by radiation treatment in all patients in three of the studies[3–5], whereas in the NSABP trial[6] one group was treated with partial mastectomy alone. The terminology and definition of the various surgical techniques in these trials (*Table 1*) clearly indicate the wide discrepancies between them with respect to handling of the tumour and overlying skin, pectoral fascia and axillary nodes. In no trial was specimen radiography used for checking radicality and only in one[6] was it required that the specimen margins were pathologically free of tumour.

Classification of partial mastectomies

A large number of designations have been given to surgical procedures aimed at removing a mammary tumour with preservation of the breast. The objective of surgery can nevertheless be referred in most instances to one of a few relatively distinct categories. These are (1) excision of the bulk of or—in most instances—the entire tumour without laying claim to microscopic radicality; (2) removal of the entire tumour with a rim of surrounding benign breast tissue in order to achieve a macroscopically (and possibly a microscopically) radical procedure, and (3) more standardized and extensive techniques with dissection outside the parenchyma and a sector-like resection of tissue from the centre to the periphery of the tumour-bearing part of the breast. The radicality of a breast-conserving technique can be checked further by specimen radiography and by macro- or microscopic classification by the

Table 1 *Description of the surgical technique in first-generation controlled clinical trials of breast-conserving treatment*

Trial	Procedure	Definition	Reference
Guy's trial	Extended tylectomy (wide excision)	Wide excision of the lump together with the surrounding breast tissue within 3 cm of palpable or visible growth Axillary nodes were not removed.	3
Milan	Quadrantectomy	Radical removal of the entire quadrant containing the carcinoma including the overlying skin and the fascia of the major pectoral muscle. All axillary nodes up to the apex of the axilla were removed.	4
Villejuif	Local excision	Removal of the tumour with a margin of 2 cm of glandular tissue. Low axillary dissection.	5
NSABP B-06	Segmental mastectomy	Resection of the tumour with removal of enough normal tissue to ensure that the specimen margins were tumour-free. Removal of the pectoral fascia or skin overlying the tumour was not required. Axillary nodes removed, at least level I and II	6

0007–1323/88/080807–04$3.00

Table 2 *Proposed classification of partial mastectomies*

Characteristic	Tumorectomy	Extended tumorectomy	Quadrantectomy	Sector resection*
Dissection in non-malignant tissue required	No	Yes	Yes	Yes
Macroscopic contamination of wound accepted	Yes	No	No	No
Ventral dissection subcutaneously	Yes/no	Yes/no	Yes	Yes
Dorsal dissection in the pectoral fascia	No	No	Yes	Yes
Periphery of the breast parenchyma included in specimen	No	No	Yes	Yes
Skin excision	No	No	Yes	Yes/no
Less excision than a quadrant accepted if allowed by tumour size	Yes	Yes	No	Yes

* The proposed, standardized procedure

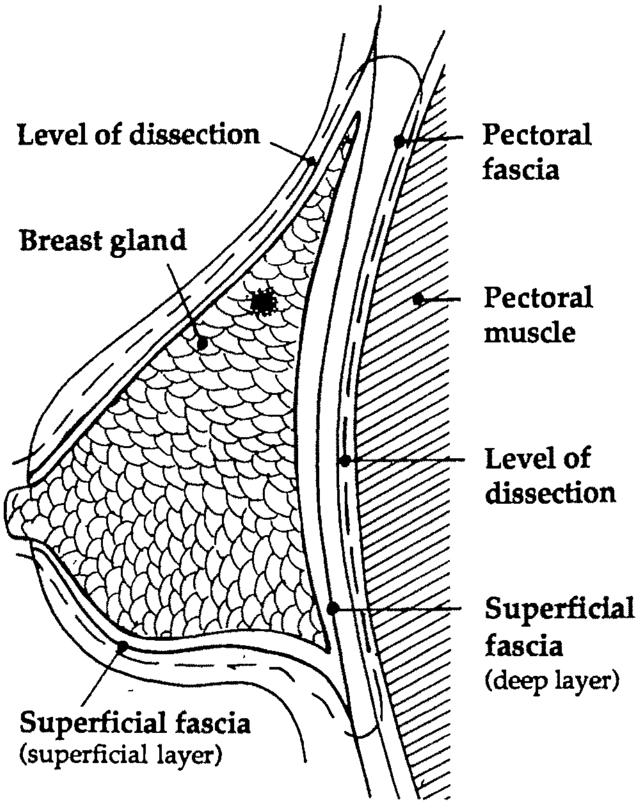


Figure 1 *Schematic view of the female breast with its fascial planes and recommended levels of dissection*

clinical pathologist. These additional means of assessing radicality are, however, part of the overall treatment strategy and handling of the patients rather than a characteristic of the surgical technique.

Proceeding from these considerations, we suggest a simple classification of the most widely used surgical procedures for breast preservation (*Table 2*). The classification of the different types of partial mastectomies is based on the objectives concerning local radicality and standardization. The term 'sector' is more appropriate than 'segment': firstly, as 'sector' is the correct geometrical term describing the shape of the excision in relation to the 'circle' of breast parenchyma; secondly, as the breast does not have any anatomical segments that are referred to in other contexts Quadrantectomy is, in fact, a special form of sector resection where the specimen includes 90 degrees of the parenchyma with a centrally located apex. We suggest that the extent of the resection should be determined by the need for macroscopic margins in relation to the tumour. In that case, the size and location (central *versus* peripheral) of the tumour will be decisive. In many instances, particularly in the treatment of a minimal screening-detected cancer, excision of a sector of less than 90° might be appropriate.

A standardized sector resection

Dorsally the anatomical boundary of the mammary gland is the pectoral fascia, and ventrally it is the superficial abdominal fascia. The latter, known to most surgeons as the fascia of Scarpa, is well recognized in operations involving the lower parts of the abdominal wall, but is usually also recognized over the breast. If the surgeon dissects the mammary gland in these two planes, the same anatomical radicality can be guaranteed ventrally and dorsally as when a mastectomy is performed.

Radicality with regard to the sides of the tumour can be obtained by choosing a suitable margin at the periphery of the cancer. The distance which is chosen, usually 1 cm or more, can be checked by perioperative palpation and by specimen radiography. This requires that the tumour can be macroscopically defined, either by palpation or by mammography, or both. When a non-palpable lesion is approached, we have found the Frank localization technique[7] easy to combine with the surgical technique described below.

The operation can be divided into the following four steps.

1. Dissection of the skin (Figure 1)

In the upper part of the breast a curvilinear incision or a radial incision is used. However, we have preferred a radial incision in the lower part of the breast and it should always be used when a reduction of the skin over the tumour is planned (in cases where a reconstruction of the breast parenchyma is to be performed and when a palpable lesion is extirpated).

The skin is dissected in the plane of the superficial fascia. The procedure is made easier if upward traction is applied to the skin margins. The edges of the tumour should be given a generous margin, leaving at least one-third of the gland dissected free from the skin. With tumours close to the areola, the milk ducts should be cut and the nipple dissected free. This avoids outward and upward retraction of the breast after wound closure. Peripherally, the dissection is brought to the palpable edge of the mammary gland.

2. Breast gland dissection (Figure 2)

At least one-third of the periphery of the breast gland is now dissected free along the plane of the pectoral fascia, which is included in the specimen. Two haemostats are applied at the periphery of the gland, which allow it to be stretched by an assistant. The dissection then proceeds between the pectoral muscle and its fascia towards the centre of the breast. In most cases the surgeon can now palpate the cancer bidigitally. When the lesion is non-palpable and a needle localization technique is used, the hook of the needle can be localized in the same way. The resection is performed with the index and middle finger underneath and the thumb above the tumour or the tip of the localization needle. In most instances the resection can be done in the form of a sector. By holding the palpable or localized tumour, the surgeon can feel the distance between the periphery of the tumour and the margin of resection.

With centrally located tumours, a central resection is performed and we have removed the nipple with the specimen. Reconstruction in these cases requires that the breast glandular

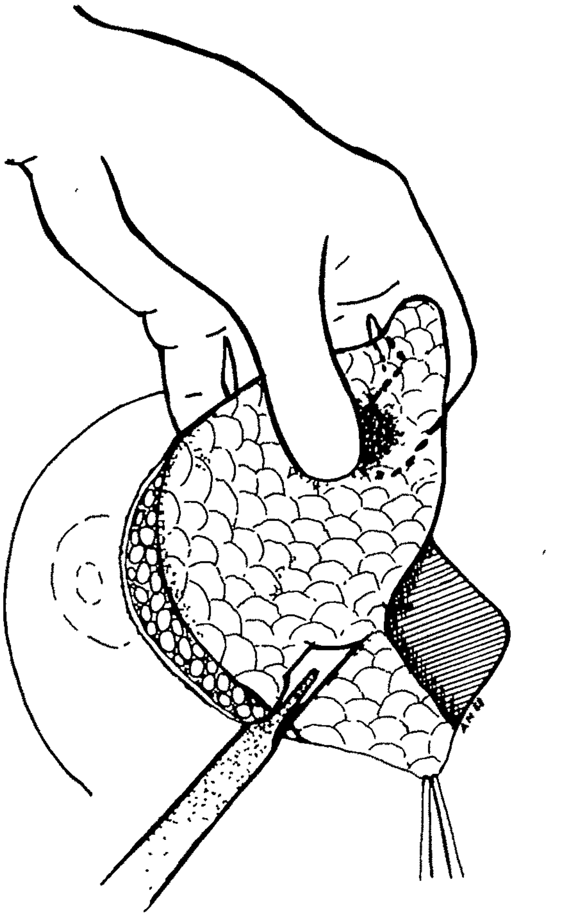


Figure 2 *The sector resection is performed with the tumour or wire hook held between the thumb and forefinger, which makes control of resection margins possible*

tissue be transposed into the defect without tension. This is done by dissecting the outer upper quadrant of the gland from the pectoral fascia and dividing the parenchyma in an oblique direction towards the axilla to be able to mobilize it into the central defect.

As the dissection is performed in defined anatomical planes, it is easy to spread out the resected specimen so that the fascia lies on the back and the subcutaneous layer faces upwards. The anatomical relation of the specimen to the breast can be clarified further by marking the central part with sutures. If the specimen is sent in this way for specimen radiography and histopathological examinations, communication (e.g. concerning tumour radicality) between the surgeon, radiologist and pathologist will be facilitated.

3 Reconstruction of the breast (Figure 3)

We have experience both in reconstructing the breast parenchyma and in leaving the operative defect open. Both techniques give a good cosmetic result. The most important detail at this stage of the operation seems to be good haemostasis, thus avoiding postoperative haematomas or seromas. If the defect is left unsutured, meticulous cautery of small arteries is preferably combined with drainage. When the parenchyma is sutured, the haemostasis is often so good that drainage can be omitted. In these instances, the wide wedge-shaped gap is closed with one layer of 3/0 polyglycolic acid sutures. Generous mobilization of the mammary gland, both ventrally and dorsally, makes the reconstruction easier

4. Dissection of the axilla

The axilla is incised transversely between the axillary vein and the visible edge of the mammary gland A separate incision in the axilla is preferred, even when the tumour is situated close to the axilla.

Discussion

The described technique has been used routinely for breast-conserving operations in two health care regions in Sweden, in one of them since 1979. In a study of postoperative complications, it was found that among 71 women who had undergone sector resection and axillary dissection, 19 (26·8 per cent) developed seromas, three (4·2 per cent) haematomas and five (7·0 per cent) wound infections[8]. In a study with a median follow-up period of 36 months after sector resection, the South Swedish Breast Group found that among 255 women with histopathologically stage I breast cancers and 31 with stage II, 4 showed recurrence in the breast[9].

The patient's own appraisal of the cosmetic result after a sector resection was recently evaluated in a questionnaire study on 285 women. The response rate was 92 per cent and 96·5 per cent of the women found the new appearance of the breast attractive or acceptable[10]. The reported rate of psychological distress due to the cosmetic outcome was 4·2 per cent. In this study both curvilinear and radial incisions were used and the breast parenchyma was not always reconstructed. These variations in the surgical technique did not significantly influence the cosmetic result according to the results of a multivariate analysis[10]

The described orientation of the specimen, the perioperative mammographic examination of the sector and the subsequent histopathological examination for radicality allow optimal local control and facilitate communication of the findings between the surgeon, pathologist and radiologist.

The multicentricity of breast cancer has been much debated as a possible contra-indication to breast-conserving therapy. The high frequency of multicentricity found in some studies

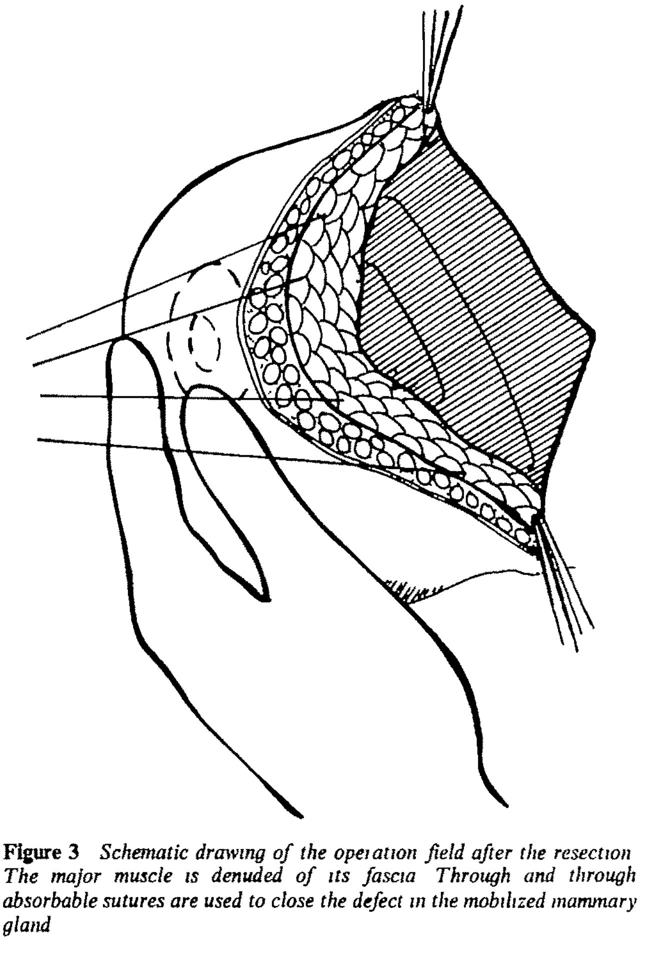


Figure 3 *Schematic drawing of the operation field after the resection The major muscle is denuded of its fascia Through and through absorbable sutures are used to close the defect in the mobilized mammary gland*

indicates that a conservative approach might leave a high frequency of 'residual' carcinoma or allegedly premalignant lesions[11]. However, the natural history of such subclinical lesions is not known[6,12] and their prevalence is probably over-estimated in pathological studies on selected patients. When clinically or mammographically overt multicentric cancers were excluded, Holland *et al.*[13] found in a series of consecutive cases that 17 per cent of the women had cancerous lesions in quadrants remote from the resected sector if the primary tumour was 2 cm or less in diameter. Gump *et al.*[14] found multicentricity in 19 per cent of a consecutive series of 657 patients with invasive ductal carcinoma; 90 per cent of the secondary foci were found in close proximity to the primary. The estimates of multicentricity in these studies are still somewhat higher than the 10 per cent incidence seen in the NSABP trial, which includes tumours up to 4 cm in diameter[12]. Most recurrences after breast-conserving therapy (86–88 per cent) occur close to the previous excision[12,15,16]. Furthermore, inadequacy of the surgical excision, intralymphatic extension and tumour size correlate with the risk of recurrence, indicating that the local surgical control of the primary tumour—checked by specimen radiography and histopathology—might be the factor of decisive importance.

In some women with multicentric mammographically malignant lesions (including diffusely spreading malignant microcalcifications), microscopic tumour is found in the resection margin despite resection in macroscopically tumour-free parenchyma. In other instances extensive multifocality or lymphatic tumour extension is revealed at the histopathological examination. In tumours with any of these characteristics, local control is probably not achieved in an acceptable proportion of the patients with breast-conserving surgical treatment alone. Likewise, it is not known whether a sector resection is sufficient when dealing with a well-defined group of malignant microcalcifications and with limited intraductal spread in the excised sector.

The main advantage of the described operative technique is that it uses well-defined anatomical landmarks, allows control of radicality, and thus gives the surgery a maximal chance of achieving the therapeutic goal of local tumour control. It is suitable for standardization, which is one of the prerequisites for generalization of a treatment when it has been evaluated in a clinical trial. A high degree of uniformity in this respect is advantageous both for the internal and external validity in a study. Regarding details such as the skin incision used in the upper part of the breast, reconstruction of the parenchyma and the use of drainage, there are no clinical data from controlled trials to support any specific surgical technique. Good cosmetic results have been reported with a variety of techniques[5,6,10,17–21].

Acknowledgements

This study was supported by grants from the Swedish Cancer Society.

References

1. Harris JR, Hellman S, Kinne DW. Limited surgery and radiotherapy for early breast cancer. *N Engl J Med* 1985, **313**: 1365–8.
2. Bluming AZ, Dosik G, Lowitz B *et al.* Treatment of primary breast cancer without mastectomy *Ann Surg* 1986; **204**: 136–47.
3. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment of early breast cancer. A report after ten years of clinical trial *Br Med J* 1972, **2**: 423–9
4. Veronesi U, Saccozzi R, Del Vecchio M *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981; **305**: 6–11.
5. Sarrazin D, Le M, Rouëssé J *et al.* Conservative treatment versus mastectomy in breast cancer tumours with macroscopic diameter of 20 millimeters or less. *Cancer* 1984; **53**· 1209–13
6. Fisher B, Bauer M, Margolese R *et al.* Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985; **312** 665–73.
7. Frank HA, Hall FM, Steer ML Preoperative localization of nonpalpable breast lesions demonstrated by mammography. *N Engl J Med* 1976, **295**. 259–60.
8. Tejler G, Aspegren K. Complications and hospital stay after surgery for breast cancer: a prospective study of 385 patients. *Br J Surg* 1985, **72**. 542–4.
9. Ewers B, Aspegren K, Borgström S. Bröstbevarande behandling vid bröstcancer i stadium I i södra sjukvårdsregionen (Breast-conserving treatment in stage I mammary cancer in the southern medical care region.) *Svenska Läkaresallskapets handlinger* (*Documents of the Swedish Society of Medical Sciences, Hygiea* 1985; **6**: 180.
10. Holmberg L, Zarén E, Adami HO, Bergström R, Burns T Patient's appraisal of cosmetic result after segmental mastectomy for benign and malignant breast tumours *Ann Surg* 1988, **207**. 189–94.
11. Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF. 'Residual' mammary carcinoma following simulated partial mastectomy. *Cancer* 1975, **35**. 739–47.
12. Fisher ER, Sass R, Fisher B *et al* Pathologic findings from the National Adjuvant Breast Project (protocol 6). II Relation of local breast recurrence to multicentricity. *Cancer* 1986; **57**· 1717–24.
13. Holland R, Veling SHJ, Mravunac M Hendrics JHCL. Histologic multifocality of Tis, T1–2 breast carcinomas Implications for clinical trials of breast-conserving surgery. *Cancer* 1985; **56**. 979–90.
14. Gump FE, Shikora S, Habit DV, Kister S, Logerto P, Estabrook A. The extent and distribution of cancer in breasts with palpable tumours *Ann Surg* 1986; **204**: 384–390.
15. Schnitt SJ, Connolly J, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early recurrence in stage I and II breast cancer treated by primary radiation therapy. *Cancer* 1984; **53**: 1049–57
16. Schnitt SJ, Connolly J, Recht A, Silver B, Harris JR Breast relapse following primary radiation therapy for early breast cancer. II. Detection, pathologic features and prognostic significance *Int J Radiat Oncol Biol Phys* 1985, **11**. 1277–84
17. Clarke D, Martinez A, Cox RS. Analysis of cosmetic results and complications in patients with stage I and II breast cancer treated by biopsy and irradiation. *Int J Radiat Oncol Biol Phys* 1983; **9**: 1807–13.
18. Pattersson MP, Pexner RD, Hill LR, Nayana LV, Desai K, Lipsett JA. Patient self-evaluation of cosmetic outcome of breast-preserving cancer treatment. *Int J Radiat Oncol Biol Phys* 1985, **11**: 1849–52.
19. Bartelink H, van Dam R, van Dongen J. Psychological effects of breast conserving therapy in comparison with radical mastectomy. *Int J Radiat Oncol Biol Phys* 1984; **11**: 381–5
20. Romdahl MM, Montague ED, Ames FC, Richards PC, Schell SR. Conservation surgery and irradiation as treatment for early breast cancer *Arch Surg* 1983; **118**· 521–8
21. Durand JC, Poljicak M, Lefranc JP, Pilleron JP. Wide excision of the tumor, axillary dissection, and postoperative radiotherapy as treatment of small breast cancers *Cancer* 1984; **53**· 2439–43.

Paper accepted 21 March 1988

Br. J. Surg. 1988, Vol. 75, August,
811–817

Application of mammary serum antigen assay in the management of breast cancer: a preliminary report

A monoclonal antibody (3E1·2) based serum test using an enzyme immunoassay has been used to determine circulating levels of the breast cancer associated antigen—mammary serum antigen (MSA). Of 157 patients with early breast cancer (stage I and II) and 199 patients with advanced breast cancer (stage III and IV), 73 per cent and 87 per cent respectively had elevated MSA levels (i.e. >300 inhibition units (IU). Furthermore, 40 of 44 patients (91 per cent) had a significant fall of MSA levels with reduction in tumour load by mastectomy. In addition, there was a correlation of MSA levels with the clinical course: changes in MSA levels correlated with changes in disease status (progressive disease, stable disease, disease regression) in 54 of 61 patients and antedated disease progression or recurrence by up to 8 months in some patients; and in 32 of 36 patients (89 per cent) with no clinical evidence of recurrence MSA levels did not vary by more than 25 per cent of the original MSA value over a period of 2–15 months. MSA is therefore a useful tumour marker in the diagnosis and staging of breast cancer. There is also evidence that serial estimations of MSA levels may be used to detect subclinical recurrence and the fluctuations in MSA levels might be useful in assessing response to therapy. Furthermore, it was also noted that surgical procedures such as fine needle aspiration biopsy or incisional biopsy could lead to a rise in MSA levels.

Keywords: Tumour markers, breast cancer, mammary serum antigen, monoclonal antibodies, serum test for breast cancer

J. J. Tjandra[*†],
I. S. Russell[†],
J. P. Collins[†],
S. A. Stacker[*] **and**
I. F. C. McKenzie[*]

[*]Research Centre for Cancer and Transplantation, Department of Pathology, The University of Melbourne, Parkville, Victoria 3052, Australia and [†]Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

Correspondence to:
Professor I. F. C. McKenzie

Carcinoma of the breast remains the leading cause of cancer mortality among women in western countries and its incidence is rising; currently every woman has a 1 in 14 chance of developing the disease during her lifetime[1]. While the natural history of untreated 'early' breast cancer remains uncertain, there has been little change in the 10-year survival rate over the past 40 years despite many innovations in therapy[2]. The cause of breast cancer is not known, so that at the present time, strategies which address early detection of the disease or recurrence enabling prompt treatment are more likely to reduce the mortality and morbidity from this disease.

Recent advances in monoclonal antibody technology in breast cancer research have led to studies that might ultimately have an impact on various areas of the management of this disease. Development of a serum test for breast cancer based on the use of a monoclonal antibody 3E1·2 was previously described[3]. The monoclonal antibody has a high degree of specificity for breast cancer and a limited reactivity with other tissues, in addition, by means of immunoscintigraphy, ^{131}I-labelled 3E1·2 has been used to localize metastases in the axillary lymph nodes of patients with breast cancer[4]. The basis of the serum test depends on the detection of an antigen (mammary serum antigen (MSA)) present on a high molecular weight glycoprotein ($M_r > 3 \times 10^5$), which has been isolated and purified from human serum but is absent from milk and human milk fat globule membranes[5]. It has been established that a low level of MSA (<300 inhibition units (IU)) was found in the serum of apparently healthy blood donors (98 per cent of the 2400 individuals) and in patients with benign breast disease (82 per cent of 40 patients). Raised MSA levels were detected in the serum of some patients (8–19 per cent) with other malignancies and a number of non-malignant diseases, such as hepatitis, cirrhosis and pancreatitis, but the levels were generally lower than in those with breast cancer[5].

We now report our preliminary results for the potential clinical application of MSA levels in the early detection of breast cancer, in the assessment of tumour burden and for monitoring disease progression and therapeutic efficacy.

Patients and methods

Serum samples

Serum samples were obtained from patients presenting at the Breast Clinic of the Royal Melbourne Hospital or at the Melbourne Private Consulting Rooms and from the Peter MacCallum Hospital, Melbourne, Australia. In all, 356 serum specimens were obtained for staging studies with patients' consent. Forty-four patients had pre- and postmastectomy MSA levels determined. Serial MSA levels were also measured in 111 patients undergoing follow-up with or without treatment (see below) between March 1986 and November 1987. Altogether there were 467 patients in the study with an age range of 22–76 years. Serum samples were obtained from clotted blood, aliquoted and stored at −70°C until use. The criteria for staging and disease status are in accordance with accepted definitions[6,7]. Information on the clinical staging and disease status was not obtained until all the MSA levels had been determined.

Detection of MSA levels by competitive enzyme immunoassay

The murine monoclonal antibody 3E1·2 was raised against fresh human breast cancer cells as described by Stacker *et al*[3]. The antigen used in the serum inhibition assay was extracted from a breast cancer cell line or from fresh breast cancer specimens by homogenization in sucrose, 0·25 M, Tris, 25 mM; EDTA, 1 mM; pH 7·4 at 4°C. The mixture was centrifuged to pellet crude membranes which were coated onto 96-well flexible PVC plates (Costar, Cambridge, Massachusetts, USA) with 50 μl 0·1 per cent glutaraldehyde at room temperature for 60 min after

0007-1323/88/080811-07$3.00

Table 1. *Reproducibility of mammary serum antigen assay*

	Serum specimen				Serum specimen		
	A	B	C		A	B	C
Intra-assay variability (3 serum samples were assayed in replicas of 9)				Interassay variability (3 serum samples were assayed 3 times, each time in replicas of 3)			
Mean (IU)	685	2118	196	Mean (IU)	575	1765	166
CV (%)	12	12·6	11·3	CV (%)	19	20	18

IU, inhibition unit, CV (%), coefficient of variation was determined from the components of variance[8]

which they were washed (PBS/0·05 per cent Tween 20) and treated with 1 per cent bovine serum albumin (BSA) for 60 min at room temperature to block protein binding sites. In a separate plate (previously coated with 1 per cent BSA), patients' sera (diluted 1/32) were incubated with purified monoclonal antibody 3E1·2 (50 ng/well) for 3 h at room temperature; 50 μl of this mixture was then transferred to the antigen-coated plates. After an overnight incubation at 4°C, the plates were washed and incubated with 50 μl of sheep anti-mouse immunoglobulin conjugated to horse-radish peroxidase (Amersham International, UK) diluted in PBS/0·05 per cent Tween 20 for 3 h at 37°C. After removing excess antibody, the colour was developed using 50 μl of 0·03 per cent ABTS (2,2'azino-di(3 ethylbenthiazoline) sulphonate) (Amersham Int., UK) and 0·02 per cent hydrogen peroxide (B.D.H. Chemicals, Poole, UK). Plates were analysed in an ELISA plate reader (Titertek Multiscan MC) at a wavelength of 405 nm and the results relayed directly into a computer for analysis (Commodore CBM 8032) using the 'CELISA' and 'DECODER' programs to convert optical density readings to inhibition units (IU).

Calculation of inhibition units

The level of mammary serum antigen in the serum was expressed as inhibition units (IU)—derived from a standard antibody curve obtained by making double dilutions of antibody 3E1·2 in the range from 200 to 1 ng/ml and measuring binding to the solid phase antigen. From this standard curve, optical density values were adjusted in the computer to correspond to a range of 1–10 000 IU so that a high level of IU corresponded to a high level of MSA in serum. To provide a standard, sera from five normal individuals were pooled for use in each assay and the MSA level of this sample adjusted to correspond to 100 IU. Using this level and the standard curve, the IU was calculated for each test sample. A level of 300 IU was determined as the upper limit of normal, based on a previous study of 2400 normal controls to give an acceptable false positive rate of <2 per cent[5], these control samples were obtained from a blood bank and were not strictly age-matched with the data presented in this study.

Results

Intra- and interassay variability

An intra-assay and interassay variability of 12 per cent and 19 per cent respectively was obtained (*Table 1*) and hence the test has reasonable reproducibility for routine clinical use.

Distribution of circulating MSA levels in patients with breast cancer

The MSA levels from patients with early (stage I and II) and advanced (stage III and IV) breast cancer are shown (*Figure 1*). Elevated MSA levels were observed in 69 per cent (61/88) of patients with stage I disease, 78 per cent (54/69) of patients with stage II disease, 82 per cent (32/39) of patients with stage III and 89 per cent (142/160) of patients with stage IV disease. The mean levels (±s.e.m.) of stage I, II, III and IV were 603±112, 982±279, 1126±367 and 3778±582 inhibition units (IU) respectively. The range of MSA values in the four groups is also shown (*Figure 1*); only 5 per cent of stage I, 14 per cent of stage II, and 21 per cent of stage III patients have levels elevated to >1500 IU, contrasting with 53 per cent of patients with stage IV disease. This indicates a direct relationship between MSA levels and staging and that patients with metastases are more likely to have raised MSA levels, and that these levels tend to be higher than those with localized disease.

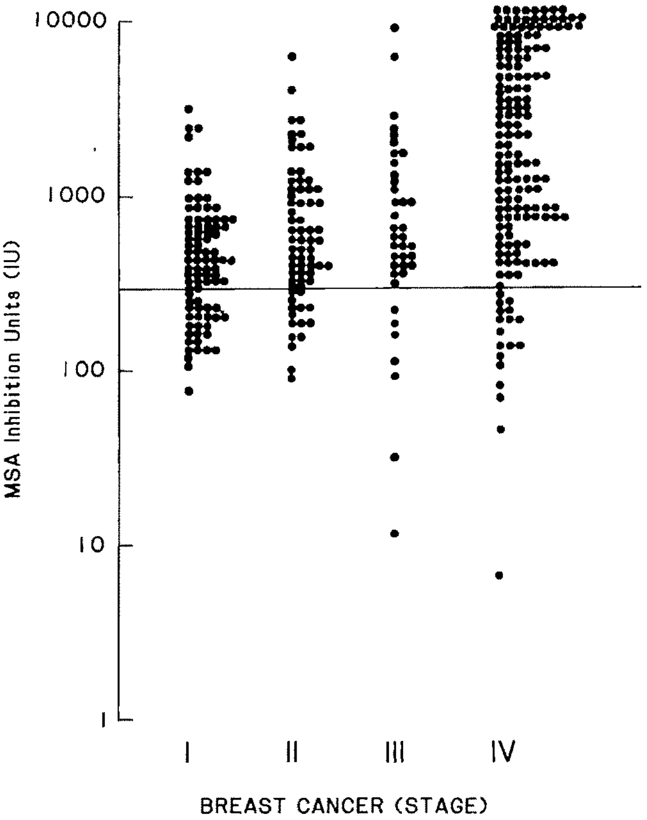


Figure 1 *Circulating MSA levels in patients with stage I, II, III and IV breast cancer. Each point represents an individual patient. The cut-off value of 300 IU is indicated by a horizontal line. MSA inhibition units are indicated by a log-scale on the vertical axis. MSA, mammary serum antigen, IU, inhibition unit*

Comparison of circulating MSA levels in patients with localized breast cancer (stages I and II) before and after mastectomy

The pre-operative and postoperative MSA levels were determined in 44 stage I and II patients who had undergone mastectomy (*Figure 2a, b*). All pre-operative MSA levels were determined within 2 weeks before surgery and all except two patients had MSA levels determined before any surgical procedure such as fine needle aspiration biopsy (FNAC), Trucut biopsy or open biopsy. Of these two patients, one had Trucut biopsy, the other FNAC before blood sampling for MSA levels (see below). Serial postoperative MSA levels were determined whenever patients were seen at intervals varying from 2 days to 6 months; this flexible protocol ensured that each patient was examined for recurrence at the time of blood sampling. None had clinical evidence of either residual disease or recurrence during the follow-up period. Of 44 patients, only 3 were followed up for <2 weeks. The first postoperative MSA levels were measured at slightly different times in the patients studied because of the flexible protocol but 38/44 patients (86 per cent) had the first postoperative levels measured between 2 weeks and 2 months after operation.

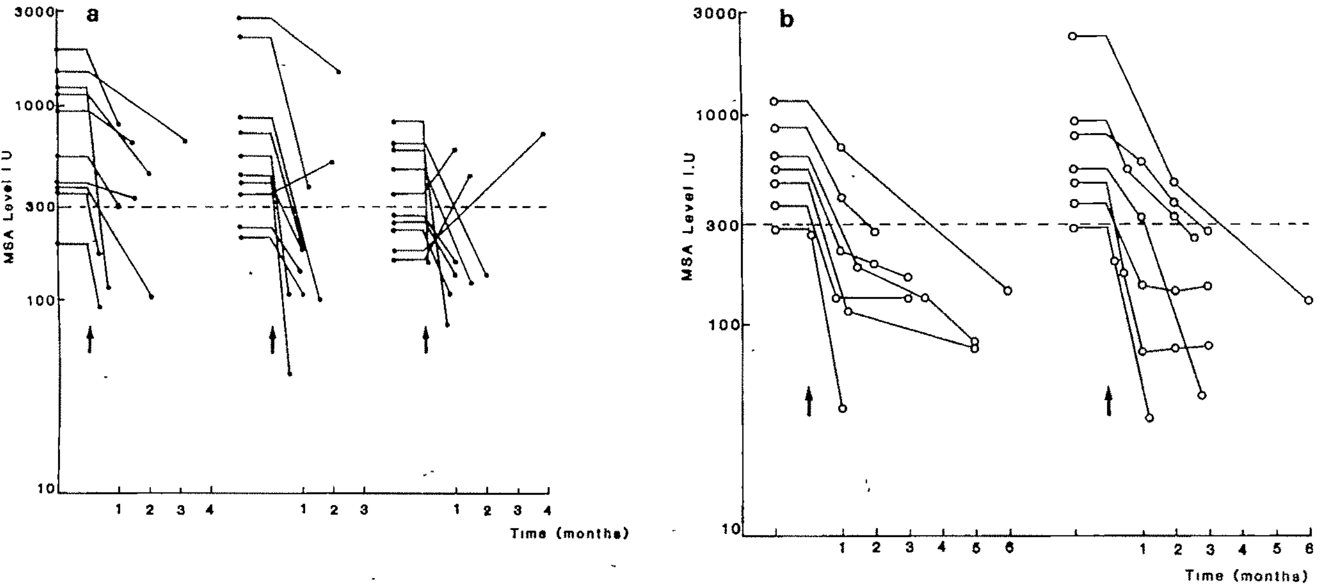


Figure 2 *Circulating MSA levels in patients with breast cancer before and after mastectomy, each line represents an individual patient. The cut-off value of 300 IU is indicated by a dotted horizontal line. The time (months) after operation is indicated on the horizontal axis.* Figure 2a *is divided into three sections for clarity. Figure 2b shows the results for the 14 patients who underwent serial postmastectomy assays. MSA, mammary serum antigen; IU, inhibition unit*

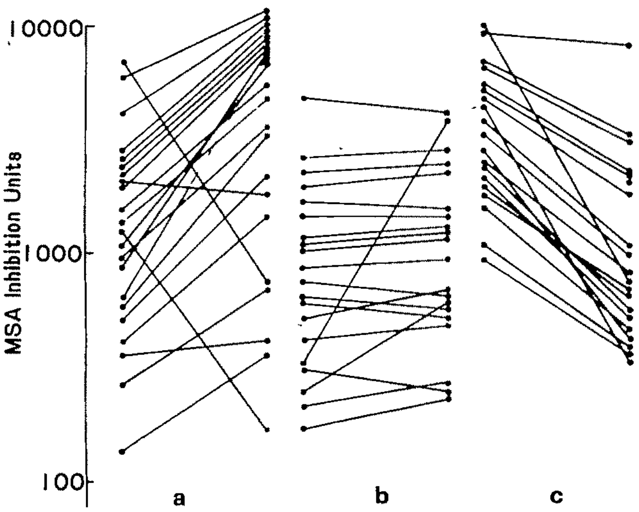


Figure 3 *Graph showing the changes in MSA levels over a period of 4–12 months in a group of 61 patients with advanced breast cancer undergoing therapy. The patients were classified as* (**a**) *progressive* (n = *22*), (**b**) *stable* (n = *20*) *or* (**c**) *regressive disease* (n = *19*). *MSA, mammary serum antigen*

MSA levels fell in 40/44 patients (91 per cent) after mastectomy, and this could be seen as early as the second day. The fall of MSA in these patients was beyond that which can be explained by interassay variability. Due to a general reluctance of patients to have repeated blood tests, serial postmastectomy levels were only obtainable from 14 patients (*Figure 2b*). The MSA levels of 9/14 patients continued to fall with time, even at 1 month postoperatively, but the MSA levels in 3 patients plateaued after 1 month. The trend in the remaining 2 patients is not clear because serial measurements were only made for 1 month after operation.

Of the 44 patients studied postoperatively, 33 (75 per cent) had MSA levels which fell below the normal cut-off level of 300 IU. Of these, eight had pre-operative levels <300 IU, and the postoperative levels showed a further decrease. A decrease in MSA levels was observed in another 7/44 patients (16 per cent) but with the postoperative level remaining above 300 IU for duration varying from 1 to 3 months after mastectomy (*Figure 2a*). The remaining four patients (9 per cent) showed a rise in MSA level despite adequate total excision of the primary tumour (*Figure 2a*). Hence the majority (91 per cent) of patients had a significant fall in their MSA levels after mastectomy, which corresponded to a reduction in tumour burden. The significance of persistently elevated postmastectomy MSA levels is, at this stage, uncertain (see Discussion).

Table 2 *Correlation of changes in disease status with mammary serum antigen levels in patients with breast cancer* (n = *61*)

	Disease status		
MSA level (IU)	Progressive	Stable	Regressive
Increased*	18	2	0
Unchanged†	2	18	1
Decreased‡	2	0	18
Total	22	20	19

MSA, mammary serum antigen; IU, inhibition unit
* Increase of >50%
† Changes in MSA levels <50%
‡ Decrease of >50%

Correlation of circulating MSA levels with the clinical course of patients

In a prospective study, the MSA levels were determined in serum samples of 61 patients with metastatic breast cancer treated and followed regularly over 4–12 month periods. *Figure 3* and *Table 2* show the results of serial MSA testing in relation to the different clinical course (progressive disease, stable disease and disease regression)[6]. For this purpose we chose to compare two values of MSA level: the value at initial evaluation and the value at the time of the change of disease status or, in the case of the group with stable disease, the value at the conclusion of the study at November 1987 (4–12 month period). A change of more than 50 per cent in MSA level was considered significant. In total, 54/61 (89 per cent) had changes in MSA levels which correlated with changes in disease status. Four patients with progressive disease did not have significant rises in their MSA levels. Two of these patients had predominantly local chest wall recurrence and the other two had rapidly progressive disease and died within 2 months of the initial change in disease status from widespread metastases. Two patients with stable disease had a significant rise in MSA levels during the study period. One of the patients with disease regression had MSA levels which remained static.

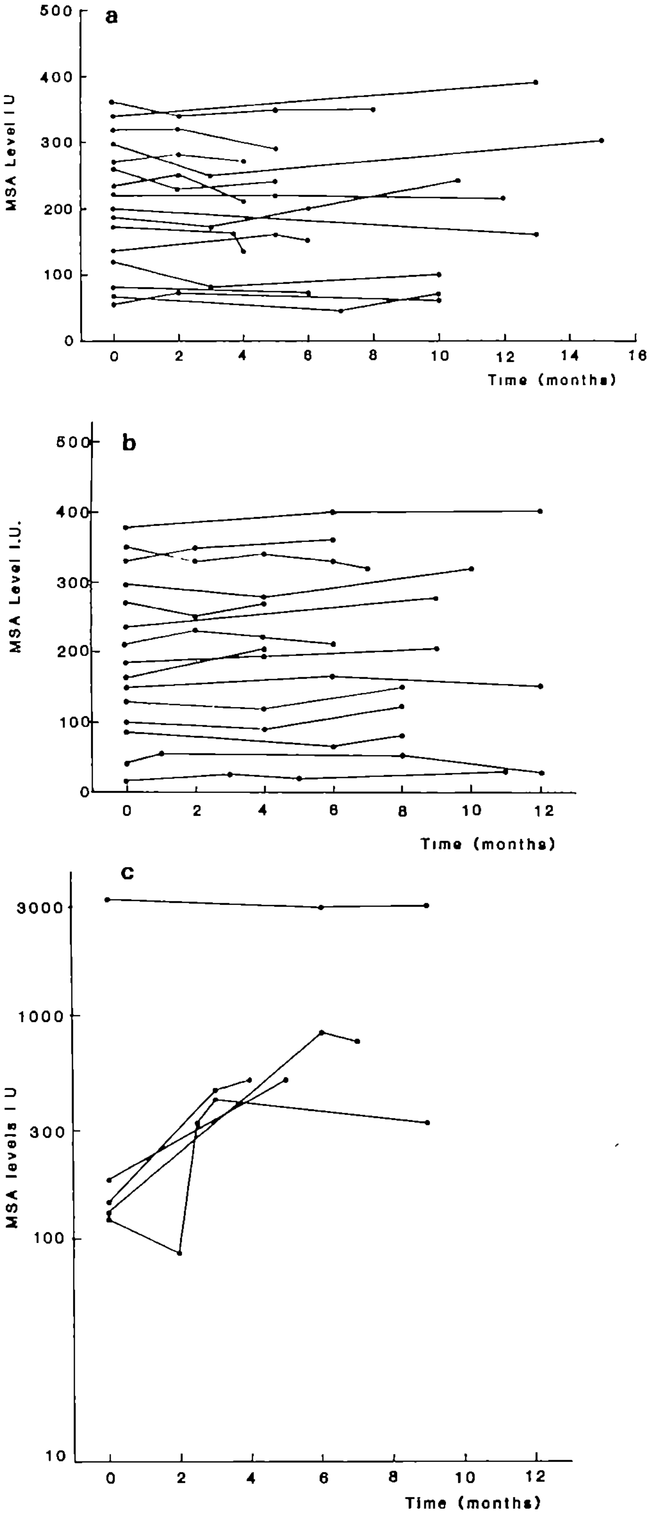


Figure 4 *Circulating MSA levels in patients who had no evidence of disease recurrence of breast cancer. These patients previoously had mastectomy. The figure is divided into three sections for clarity. Each line represents an individual patient. MSA, mammary serum antigen; NED, no evidence of disease recurrence*

MSA levels in patients with no clinical evidence of recurrence of breast cancer

Thirty-six patients who had had a mastectomy were also examined and their MSA measured (*Figure 4a*, *b* and *c*), these were all patients who had been assessed as having no evidence of recurrence (NED) of breast cancer by clinical assessment and conventional investigations. They were selected because they all had had mastectomy at least 3 months previously and had been followed in the clinic between March 1986 and November 1987. Three months were allowed to elapse to allow stabilization of MSA levels postoperatively. The duration of MSA follow-up ranged from 4 to 15 months, and 27 patients (75 per cent) were followed for at least 6 months. Allowing for interassay variability (19 per cent), 32/36 (89 per cent) of patients with NED had MSA levels that did not vary by more than ±25 per cent of the original MSA value. However, 4/36 (11 per cent) of patients showed a rise in MSA levels (*Figure 4c*) although, clinically, they remained free of disease and had had adequate surgery in the first instance. Thus serial MSA levels correlated with the clinical status of 32/36 patients (89 per cent) with no clinical evidence of disease.

Correlation of changes in circulating MSA levels with clinical disease progression or recurrence

In a retrospective analysis of 36 patients (11 with NED, 25 with stable disease who all subsequently developed recurrence or progression of disease diagnosed by clinical examination or by investigations), the changes in MSA levels (a change of >50 per cent was considered significant) were correlated with clinical changes (*Figure 5*). While in the great majority (20/36) the changes in MSA levels occurred about the same time as clinical changes; in 12/36 patients the changes in MSA levels preceded changes in disease status sometimes by as much as 8 months (*Figure 5*). In 4/36 patients, however, the clinical disease progression preceded any changes in MSA levels; the MSA levels fell in two of these patients and remained unchanged in the other two patients despite progression of disease. Representative examples of this retrospective study are described.

Patient 1 (Figure 6a). A patient with advanced breast cancer was treated with chemotherapy and was considered to be clinically stable, despite rising MSA levels over a period of 7 months. It was not until 7 months had elapsed before it became obvious that the disease had progressed.

Patient 2 (Figure 6b). This patient had had right Patey mastectomy for stage II breast cancer, and remained disease free until she presented with local recurrence and bony metastases. Chemotherapy was commenced with a partial clinical response over the following 2 months and a corresponding fall in the MSA level. Chemotherapy was subsequently stopped for 3 weeks owing to chemotherapy-induced neutropenia, during which time there was disease progression with a corresponding rise of MSA level. Chemotherapy was subsequently restarted with a rapid arrest of disease progression and with a corresponding fall in the MSA level. Over the following 7

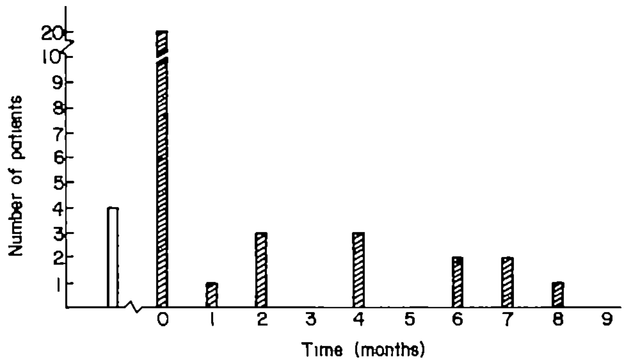


Figure 5 *Comparison of the change in MSA levels with clinical disease progression and recurrence. The time (months) of MSA rise before clinical changes is shown on the horizontal axis. Time 0 indicates that the rise in MSA levels occurred at the same time as documented clinical changes. The number of patients is indicated on the vertical axis.* ■, *patients who had a rise in MSA levels* ☐, *patients who did not have a rise in MSA levels despite progression of disease; MSA, mammary serum antigen*

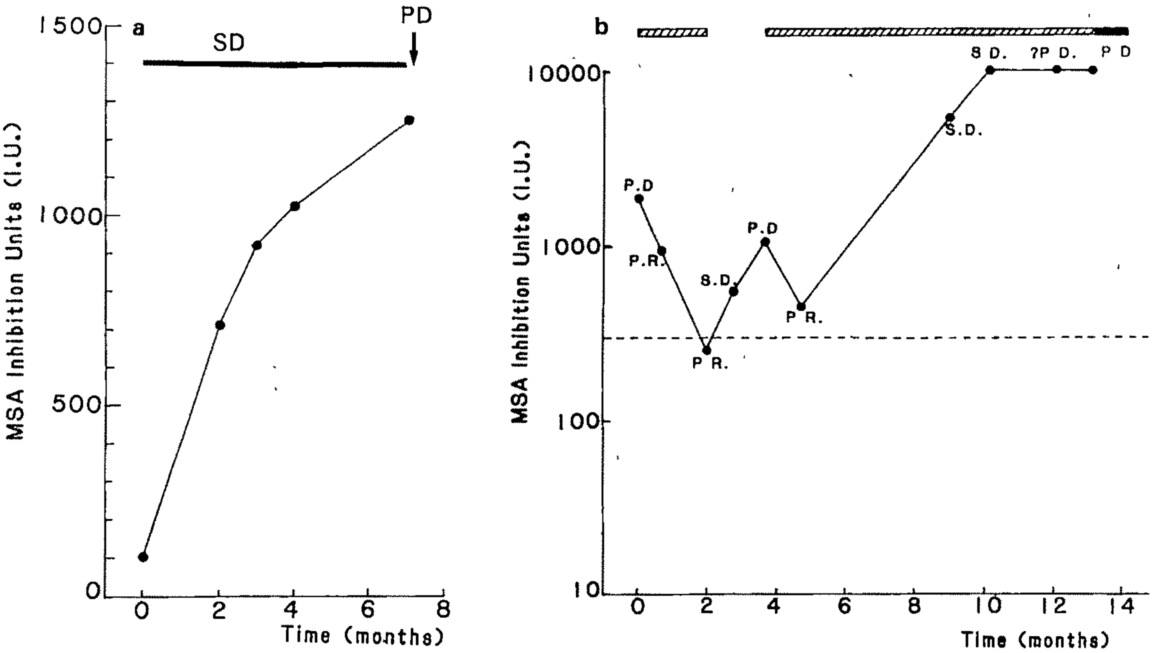


Figure 6 *Monitoring the clinical course of a patient with advanced breast cancer by MSA assay* ▨ *and* ■, *duration of therapy with different chemotherapeutic agents, MSA, mammary serum antigen, PD, progressive disease, SD, stable disease, PR, partial response*

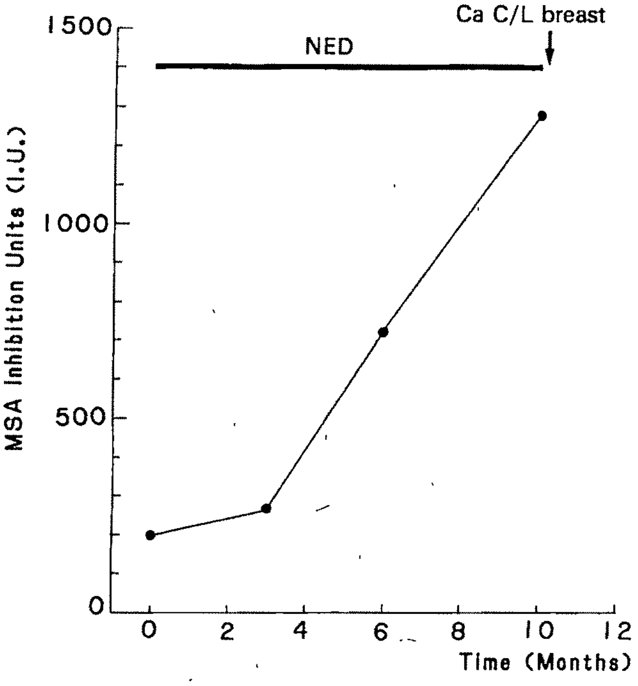


Figure 7 *Monitoring the clinical course of a patient with no clinical evidence of recurrence by MSA assay* ——, *the period of NED; MSA, mammary serum antigen, NED, no clinical evidence of recurrence*

months, the MSA level continued to rise although clinically the disease remained stable. It was not until 7 months after MSA levels began to rise that there was clinical evidence of progression of disease leading to a change of the chemotherapy.

Patient 3 (Figure 7). A patient, who had undergone Patey mastectomy several years ago and had been clinically free of disease, was followed over a 10-month period. Rising MSA levels were noted, although clinically the patient was free from disease. Ten months later a new carcinoma in the contralateral breast was noted.

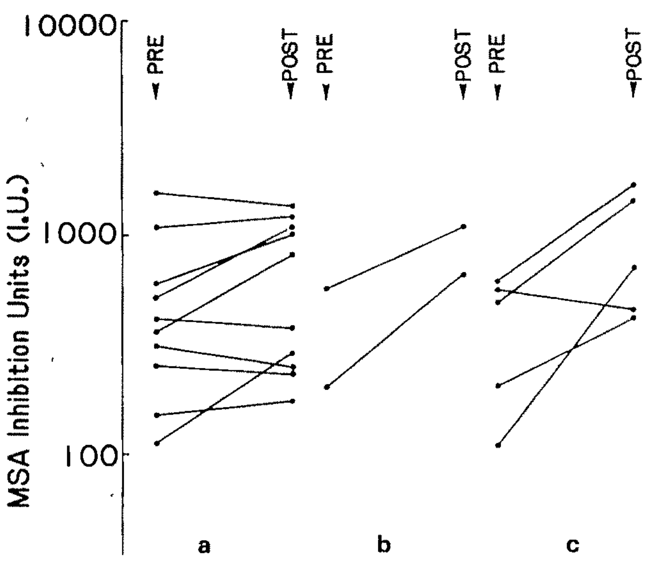


Figure 8 *Circulating MSA levels in patients with breast cancer before (pre) and after (post) surgical intervention:* (**a**) *FNAC,* (**b**) *Trucut biopsy,* (**c**) *open incisional biopsy. Each line indicates a patient MSA, mammary serum antigen, FNAC, fine needle aspiration biopsy*

Effect of FNAC, Trucut biopsy and open breast biopsy on MSA levels in breast cancer patients

MSA levels were determined before and 1–2 weeks after FNAC in 10 patients, Trucut biopsy in 2 patients, and incisional breast lump biopsy in 5 patients in a prospective study (*Figure 8*). Four of 10 patients had a significant rise (> 50 per cent) in MSA levels after FNAC, 2/2 patients after Trucut biopsy and 4/5 patients after incisional breast lump biopsy.

Discussion

Several tumour markers have been shown to be elevated in association with breast cancer, including oncofetal products carcino-embryonic antigen (CEA), hormones (calcitonin and β-human chorionic gonadotrophin, enzymes (sialyl transferases and placental alkaline phosphatase), nucleosides, polyamines, acute phase protein, β_2-microglobulin and CA15-3 (a recently introduced immunoradiometric assay using monoclonal antibodies)[9–11]. However, as yet, none has gained widespread clinical use in this disease. Some, like CEA, CA15-3 and β_2-microglobulin, are limited by their sensitivity, especially in localized breast cancer[10,11]. The present study demonstrates that, based on published data, MSA is significantly more sensitive than the other available tumour markers, especially in localized breast cancer[5,10,11]. The level of MSA correlates with the staging of the disease with a tendency towards higher levels with increasing tumour burden (*Figure 1*). However, elevation of MSA level, usually to a lower level than that found in breast cancer, has been shown to occur in a proportion (18 per cent) of patients with benign breast disease and diseases other than breast cancer, and in 1·9 per cent of normal subjects[5]. It is our intention to continue to follow these normal individuals and patients with benign breast disease with raised MSA levels to evaluate the significance of the rise, but at this time none appears to have breast cancer.

Based on a small number ($n = 44$) of patients, we established that MSA levels fell in most patients (91 per cent) after mastectomy, irrespective of the pre-operative levels. In one patient, the fall in MSA level occurred within 2 days and in 9/14 patients serially followed, the levels continued to fall even at 1 month postoperatively. The precise kinetics of MSA metabolism remain to be elucidated but the precipitous fall in MSA levels after mastectomy supports the claim that MSA level is an index of tumour burden. However, it should be noted that the MSA levels in 7/44 patients (16 per cent) had not fallen below 300 IU 1–3 months postoperatively despite adequate surgery with no clinical evidence of residual disease or recurrence. Of these seven patients, four had partial mastectomy with axillary dissection while the other three patients had Patey mastectomy and it remains to be seen if the MSA levels will fall with time. However, one cannot exclude the possibility of co-existent carcinoma *in situ* or an occult invasive cancer in the rest of the breast[12] to account for persistently raised MSA levels in those patients who only had partial mastectomy. There is, however, an intrinsic problem with the specificity of the assay with elevation of MSA to moderate levels in benign breast disease (18 per cent), other diseases (8–19 per cent) and in 1·9 per cent of normals. Definite conclusions can only be drawn from a larger series with longer follow-up.

There was a good correlation (89 per cent) of MSA levels with changes in disease status (progressive disease, stable disease and disease regression) (*Figure 3*, *Table 2*). Of the four patients who failed to have a rise in MSA levels despite disease progression, 2/4 had rapidly falling MSA levels with rapid disease progression and death. It is possible that this was due to anaplastic change of the tumour with resultant failure to produce MSA, although this has not been proven by immunohistochemical examination of the tumour tissue.

It was also established that, within the limits of interassay variability , the MSA levels remained stable (between 75 and 125 per cent of the original value) in 32/36 patients (89 per cent) who clinically had no evidence of recurrence over a period of 4–15 months. All these women had had mastectomy at least 3 months previously—3 months being chosen to allow stabilization of MSA levels postoperatively. As discussed above, it is known that in some patients the MSA levels continue to fall even 1 month after mastectomy (*Figure 2b*). In 4/36 patients (11 per cent), the MSA levels rose in the absence of clinical recurrence over the 4–9 months of the study period. One patient also had persistently elevated but static MSA levels (3000 IU) in the absence of recurrence over 9 months of the study period. The clinical significance of these findings is, at this stage, uncertain and follow-up of these patients will be of interest to see whether the elevated MSA levels indicate recurrent disease not yet clinically detectable. In a retrospective analysis (*Figure 5*), it was established that changes in MSA levels may precede clinical disease progression or recurrence by several months in some patients (12/36) although in the great majority of the patients (20/36) the changes in MSA levels occurred at the same time as clinical changes. There was an inherent bias against the serum test in a study of this nature, because MSA assay was only performed at the time of each clinical visit and the frequency of such visits and hence serum tests depend on the clinical judgement of the clinicians attending the patients. These results are, nevertheless, encouraging and suggest that serial estimations of MSA levels could be used either to detect subclinical recurrence or, alternatively, the fluctuations in the MSA levels might be used to assess response to treatment. It will require more patients and longer periods of follow-up in a prospective study before we can be certain if a rise in MSA level may truly antedate conventional clinical assessment in diagnosing early recurrence or subclinical disease progression.

The MSA assay detects 73 per cent of stage I and II breast cancer patients and is a relatively sensitive assay even in localized breast cancer. The correlation of MSA levels with tumour burden is apparent when one considers that the MSA levels rise with the extent of disease, fall with mastectomy, remain static in most patients with no clinical evidence of disease, change in parallel with changes in disease status and may even precede clinical changes. As such, it might be a most useful tumour marker for following the clinical course and assessing the extent of breast cancer. The early evidence that MSA changes may precede clinical changes suggests that it might also detect subclinical recurrence.

It has yet to be determined what role MSA will play as an early diagnostic test in the screening of large numbers of asymptomatic individuals. This must be considered in the context of the 27 per cent false negative rate with respect to stage I and II patients (*Figure 1*) and the previously established 18 per cent false positive rate in patients with benign breast disease and other non-breast diseases[5]. We are currently comparing the sensitivity and specificity of MSA with results obtained by mammography, and with both modalities combined. Currently, the established method of mass screening is mammography with or without breast self-examination. Mammography has limitations as its use demands a high level of expertise. There are false positives and false negatives and it may be of limited value in the dense breast. There are the added problems of cost and radiation[13–15]. It may be possible to supplement mammography with the MSA assay, which is a relatively simple enzyme immunoassay.

The present study also determined the effects of FNAC, Trucut biopsy and incomplete excision of tumour on the MSA levels We have demonstrated in 10/17 patients a surge in MSA levels greater than 50 per cent after such surgical procedures (*Figure 8*). It is possible that surgical trauma releases tumour antigen into the bloodstream. The safety of FNAC with regard to the possible risk of inducing local and metastatic tumour dissemination has been controversial but any objection to its use has been largely regarded as philosophical rather than practical[16–18]. The observation of rises in MSA levels with FNAC raises questions which are currently being studied.

In conclusion, MSA is an important tumour marker in breast cancer. The assay is simple, cheap, sensitive and reasonably reproducible. However, its precise application in routine surgical practice will take some time to establish.

Acknowledgements

The authors would like to thank K Greenaway and M. Pica for their technical assistance and R. Godding for her secretarial assistance.

References

1. Kelsey JL A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979, 1: 74–109
2. Baum M Carcinoma of the breast. In: Taylor S, ed. *Recent Advances in Surgery 10* New York: Churchill Livingstone, 1980: 241–57.
3. Stacker SA, Thompson CH, Riglar C, McKenzie IFC. A new breast carcinoma antigen defined by a monoclonal antibody. *J Natl Cancer Inst* 1985, 75 801–11

4. Thompson CH, Lichtenstein M, Stacker SA *et al.* Immunoscintigraphy for detection of lymph node metastases from breast cancer. *Lancet* 1984; **i**: 1245–7.
5. Stacker SA, Sacks NPM, Thompson CH *et al.* A serum test for the diagnosis and monitoring of the progress of breast cancer. In: Ceriani RL, ed. *Immunological Approaches to the Diagnosis and Therapy of Breast Cancer.* New York: Plenum Press, 1987: 217–27.
6. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
7. American Joint Committee on Staging. Manual for staging of cancer. 2nd ed. Philadelphia: Lippincott, 1983:
8. Snedecor GW, Cochran WG. *Statistical Methods.* 7th ed. Ames, Iowa: The Iowa State University Press, 1980: 238–54.
9. Slevin ML. Assessing response to systemic therapy. In: Stoll BA, ed. *Breast Cancer Treatment and Prognosis.* Oxford: Blackwell Scientific Publications, 1986: 264–76.
10. Hayes DF, Zurawski VR Jr, Kufe DW. Comparison of circulating CA15-3 and carcinoembryonic antigen levels in patients with breast cancer. *J Clin Oncol* 1986; **4**: 1542–50.
11. Kimber CL, Stomski FC, Blunden RW. Cancer of the breast and Beta 2 microglobulin. *Pathology* 1987; **19**: 67–70.
12. Cahill CJ, Gibbs NM, Boucter PS, Brient MJ, Price JL. Invasive breast cancer—the tip of an iceberg. *Ann R Coll Surg Engl* 1983; **65**: 356–9.
13. McCaffrey JF. Mammographic screening for breast cancer. *Cancer Forum* 1987; **11**: 5–6.
14. Langlands, AO. Mammography—where now? *Cancer Forum* 1987; **11**: 2–5.
15. Upton AC, Beebe GW, Brown JM, Quimby EH, Stellaberger C. Report of NCI ad hoc working group on the risks associated with mammography in mass screening for the detection of breast cancer. *J Natl Cancer Inst* 1977; **59**: 481–93.
16. Fox CH. Innovations in medical diagnosis—the Scandinavian curiosity. *Lancet* 1979; **i**: 1387–8.
17. Engzell U, Esposti PL, Rubio C, Sigurdoon A, Zajicek J. Investigation on tumour spread in connection with aspiration biopsy. *Acta Radiologica Therapy Physics Biology* 1971; **10**: 1–14.
18. Ferruci JT, Wittenberg J, Margolios MN, Carey RW. Malignant seeding of the tract after thin needle aspiration biopsy. *Radiology* 1979; **130**: 345–6.

Paper accepted 11 February 1988

Surgical workshop

Br. J. Surg. 1988, Vol. 75, August, 817

Superior laryngeal nerve injury: an overlooked entity in the surgery of the head and neck

K. Bevan, M. V. Griffiths and M. H. Morgan

Departments of Otolaryngology and Neurophysiology, Bristol Royal Infirmary, Bristol BS2 8HW, UK
Correspondence to: Mr K. Bevan, 70 Swallow Park, Thornbury, Bristol BS12 1LU, UK

Superior laryngeal nerve (SLN) paralysis was first described in 1906 by Mygind[1], but even today surgical injury to this nerve may go unnoticed[2]. This is because it does not always have the dramatic effects which are seen following damage to the recurrent laryngeal nerve. In addition, the clinical manifestations are variable; the laryngoscopic findings are often inconclusive with resulting controversy[3] in their interpretation.

Kark *et al.*[4] reported a 25 per cent incidence of permanent voice changes after subtotal thyroidectomy and an incidence of 11 per cent after lobectomy in their study of 325 patients. When the external laryngeal nerves were identified and preserved, permanent voice changes occurred in only 5 per cent of cases. Similar incidences of voice change have been noted after carotid endarterectomy[5–7].

With such a relatively high incidence of suspected SLN injury reported and the often inconclusive observations made with the conventional method of examining the larynx, a more reliable assessment of nerve function using techniques already available was considered appropriate.

Methods

1. Videofibrolaryngoscopic recording of the vocal cord movements;
2. Electromyographic (EMG) recordings of the cricothyroid muscle potentials and SLN evoked response: electroneurography (ENG).

A 3·6 Olympus ENF-P2 flexible rhino-laryngoscope, which is attached to a JVC GX-N8 colour video-camera, is inserted through an anaesthetized nasal passage under colour monitor control. Local anaesthetic is not required in the throat. The patient tolerates the instrument well. There is no restriction to vocal cord movements and phonation including singing can be recorded.

Action potentials from the cricothyroid muscle are obtained at rest and on phonation by inserting a fine concentric needle electrode 1 cm off the midline at cricoid level and advancing the needle superolaterally until sharply outlined units are obtained on phonation. Stimulation of the nerve at hyoid level by surface bipolar electrodes produces evoked potentials which are picked up by the concentric needle electrode positioned in the cricothyroid muscle. The cricothyroid muscle action potentials, and evoked potentials obtained on stimulation of the SLN are recorded on a 4-channel EMG machine with an additional facility to obtain permanent recordings on magnetic tape[8].

Results

In the presence of SLN palsy there may be good glottic closure but lack of tension in the affected cord with obliquity of the glottic aperture suggesting loss of cricothyroid function. During phonation, the affected cord becomes bowed and may appear shortened as the vocal process is pulled forward by the unopposed action of the ipsilateral thyro-arytenoid muscle. Pooling of saliva in the pyriform fossa suggests loss of sensation.

Needle sampling may indicate a denervated cricothyroid muscle, revealing fibrillation potentials at rest, and reduced interference pattern with variable action potentials on phonation. The affected SLN will have a prolonged latency and a low amplitude on stimulation.

References

1. Mygind H. Die Paralyse de Musculus Cricothyroideus. *Arch Laryngol* 1906; **18**: 403–13.
2. Ward PH, Berci G, Calcaterra TC. Superior laryngeal nerve paralysis: an often overlooked entity. *Trans Am Acad Ophthalmol Otolaryngol* 1977; **84**: 78–89.
3. Abelson TI, Tucker HM. Laryngeal findings in superior laryngeal nerve paralysis: a controversy. *Otolaryngol Head Neck Surg* 1981; **89**: 463–70.
4. Kark AE, Kissin MW, Auerbach R, Meikle M. Voice changes after thyroidectomy: role of the external laryngeal nerve. *Br Med J* 1984; **289**: 1412–15.
5. Dehn TCB, Taylor GW. Cranial and cervical nerve damage associated with carotid endarterectomy. *Br J Surg* 1983; **70**: 365–8.
6. Evans WE, Mendelowitz DS, Liapis C, Wolfe V, Florence CL. Motor speech deficit following carotid endarterectomy. *Ann Surg* 1982; **196**: 461–3.
7. Aldoori MI, Baird RN. Local neurological complication during carotid endarterectomy. *J Cardiovasc Surg*, in press.
8. Bevan K, Morgan MH, Griffiths MV. The role and techniques of laryngeal electromyography. *Clin Otolaryngol*, in press.

Paper accepted 29 March 1988

0007-1323/88/080817–01$3.00

Case report

Br. J. Surg. 1988, Vol. 75, August, 818–819

Lympho-epithelial 'branchial' cysts within the parotid gland

A. Wyman, L. K. Dunn*, V. R. Talati† and K. Rogers

*University Department of Surgery and *Department of Pathology, Northern General Hospital, Sheffield S5 7AU, and †Ear, Nose and Throat Department, Chesterfield and North Derbyshire Royal Hospital, Chesterfield S44 5BL, UK*

Correspondence to: Mr A. Wyman

A branchial cyst occurring within the parotid gland is a rare anomaly. Most previously reported cases have presented as a painless swelling within the parotid gland. They are usually misdiagnosed as a parotid tumour and the true nature of the lesion is only discovered at surgery. We report two such cases.

Patients

Case 1

A 44-year-old man presented with an asymptomatic 3 cm × 2 cm swelling in his left parotid gland. It had been present for 2 months. The facial nerve was intact. A diagnosis of a parotid tumour was made. He underwent superficial parotidectomy. Histological examination showed normal parotid tissue surrounding a cyst. The cyst was lined by stratified squamous epithelium containing keratin and had a further lining of lymphoid tissue. The appearances were those of a branchial cyst.

Case 2

A 71-year-old man was referred with a 5-month history of a 4 cm × 4 cm painless swelling on the right side of his face. A parotid tumour was diagnosed. The facial nerve was intact. During exploration the swelling was found to be cystic and was easily enucleated. Superficial parotidectomy was unnecessary. Histologically the appearances were those of a branchial cyst.

Discussion

The branchial cyst most frequently occurs anterior to the upper third of the sternomastoid muscle. Less common sites include any part of the lower two-thirds of the sternomastoid muscle, at the angle of the mandible, in the submandibular area or occasionally in relationship to the carotid vessels. The peak incidence is in the third decade and there is a slight male predominance. The cysts vary in size from that of a normal lymph node to several centimetres in diameter. Fluctuations in size do occur, often in association with an upper respiratory tract infection. Characteristically a branchial cyst is lined by a stratified squamous epithelium, a pseudostratified columnar epithelium or a combination of both. Beneath the lining epithelium varying amounts of lymphoid tissue are found.

The earliest report of a branchial cyst occurring within the parotid gland was by Hildebrant in 1895[1]. Since then there have been over 70 reported cases and Richardson *et al.* found 16 branchial cysts in a series of 708 parotidectomies[2]. Benign parotid tumour was the commonest pre-operative clinical diagnosis. Only two cases of associated facial nerve paralysis have been reported[3,4]. All but one of the reported cases have been unilateral[5].

All the reported cases have been treated by complete surgical excision and to date no recurrences have been described. As the usual pre-operative diagnosis was that of a parotid tumour, the commonest surgical procedure was superficial parotidectomy. Where the nature of the swelling had been determined pre-operatively or perioperatively careful enucleation of the cyst has been successfully performed[6].

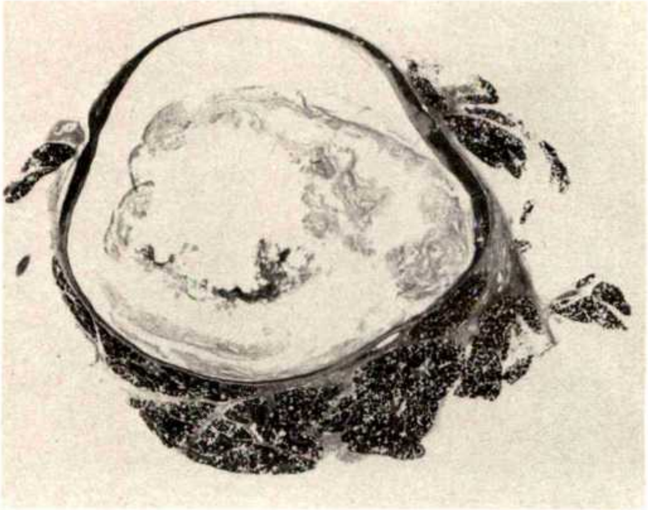


Figure 1 *Photomicrograph showing in cross-section a branchial cyst with surrounding parotid gland tissue: Case 1 (haematoxylin and eosin)*

The aetiology of branchial cysts is controversial. The more popular theories implicate the branchial apparatus, epithelial inclusions within developing lymph nodes, the thymic duct and the cervical sinus of His.

Branchial hypothesis

The development of a branchial cyst from the remnants of branchial clefts or pouches has been a generally accepted explanation for many years, mainly because of the authority given to this theory by respected clinicians and embryologists[7,8]. The relevant evidence to support this view includes the anatomical location of the cysts and the presence of sinuses and fistulae which are also explained by the same theory. The fact that a number of cysts are lined by a pseudostratified columnar ciliated (respiratory) epithelium is said to confirm their origin from the endoderm of the branchial pouch[9]. Theoretically by this hypothesis the second branchial arch is the most likely source of the branchial cyst, with the exception of the intraparotid cyst which may be accounted for by a first arch anomaly[10,11].

There are several strong arguments against the branchial hypothesis. The cysts are rarely seen at birth, unlike the branchial fistula, and usually present in later life. It is also unusual for a cyst to be connected to the pharynx or skin. The constant finding of lymphoid tissue within the wall of the cyst is difficult to explain embryologically. The branchial clefts disappear between the 32nd and 45th day[12]; any cyst would have to be formed by the end of this period. However, cervical lymphoid tissue does not begin to develop until the second month and is not easily identified until the third month[12]. The occasional fluctuations in size of a branchial cyst in association with local inflammatory conditions are also difficult to explain by the branchial hypothesis. It has been suggested that the second branchial arch cannot leave remnants in the neck below the level of the hyoid bone[13,14]. If this is true then a significant number of branchial cysts cannot be explained by this theory.

Lymph node hypothesis

Bhaskar and Bernier[15] suggested that the majority of branchial cysts arise from cystic alterations of epithelium trapped in cervical lymph nodes. After examining 468 specimens of

0007–1323/88/080818–02$3.00 © 1988 Butterworth & Co (Publishers) Ltd

branchial cysts they concluded that the epithelium was of glandular origin and was most likely to have arisen from the developing parotid gland. King[16] also rejected the branchiogenic theory and noting the close association of the cysts with lymphoid tissue suggested the term benign lympho-epithelial cyst. Supporting evidence for the lymph node hypothesis are the following observations. First, that branchial cysts are most commonly found in the upper third of the neck where parotid epithelial inclusions are most likely to occur. Secondly, salivary gland tumours also arise in this epithelium and Warthin's tumour has been found in cervical lymph nodes distant from the salivary glands[17]. Thirdly, the parotid gland and cervical lymph nodes develop *in utero* at the same time, from the second month onwards[12]. The fetus has no recognizable neck and therefore the developing parotid gland, which at this time has no definite capsule, is in close association with developing lymph nodes. Finally there is the rare finding of a branchial cyst within the parotid gland as reported here.

Little and Rickles[9,18] dispute this conclusion and favour the branchiogenic theory. They argue that if the parotid gland epithelium were implicated then the cyst should occur with a higher frequency in or around the parotid gland where the majority of lymph node epithelial inclusions are seen. Those branchial cysts found in or around the parotid gland may arise from epithelial remnants of the first branchial groove or pouch. In one study[9] they found that approximately 18 per cent of branchial cysts were lined by a pseudostratified columnar ciliated (respiratory) epithelium, which is not known to arise from parotid epithelium, but is easily explained by a branchial pouch origin. Their final argument is that the association of branchial structures with lymphoid tissue is not uncommon, e.g. the Eustachian tube and the pharangeal and lingual tonsils, and it is therefore conceivable that remnants of the branchial apparatus could be trapped within developing lymph nodes and later undergo a cystic change.

Thymic duct hypothesis

In 1913 Wengelowski[14], after examining human cadavers and embryos, concluded that no adult structures below the level of the hyoid bone could be derived from the branchial apparatus. He suggested that the branchial cyst originated from the thymus during its descent into the neck. A small number of cysts do have Hassal's corpuscles in their wall and the cysts do also occur in the neck below the hyoid bone, however the absence of recognizable thymic tissue in the majority of cysts and the predominant distribution of cysts in the upper part of the neck do not support this concept.

Thus, in conclusion, the true origin of the branchial cyst remains unknown. Cysts within the parotid gland and upper neck probably arise from parotid gland inclusions within developing lymph nodes. Cysts arising between the angle of the mandible and the hyoid bone may arise from parotid gland inclusions or equally possibly from the branchial apparatus. The term 'branchial cyst' implies a specific embryological origin and as this fact is controversial a more appropriate term would be a benign lympho-epithelial cyst.

While the aetiology of these cysts is controversial the treatment is not. The correct management is complete surgical excision. Cysts within the parotid gland may be enucleated but the diagnosis is seldom made pre-operatively and therefore superficial parotidectomy is the usual form of treatment. Recurrence following complete surgical excision has not been reported.

References

1. Hildebrant O. Über angeborene epitheliale Cysten und Fisteln des Halses. *Arch Klin Chir* 1895; **49**: 167–97.
2. Richardson GS, Clairmont AA, Erickson ER. Cystic lesions of the parotid gland. *Plast Reconstr Surg* 1978; **61**: 364–70.
3. Miglets AW. Parotid branchial cleft cyst with facial paralysis. *Arch Otolaryngol* 1975; **101**: 637–8.
4. Pensak ML, Casuccio JR, Lesnick TH, Sasaki CT. Facial paralysis resulting from parotid branchial cyst. *Otolaryngol Head Neck Surg* 1982; **90**: 676–8.
5. Moore T. Congenital cysts of the parotid gland. *Lancet* 1940; **i**: 168–9.
6. Fujibayashi T, Itoh H. Lymphoepithelial cyst within the parotid gland. *Int J Oral Surg* 1981; **10**: 283–92.
7. Rains AJH, Ritchie HD. *Bailey and Love's Short Practice of Surgery*, 19th ed. London: Lewis, 1984: 595.
8. Sadler TW. *Langman's Medical Embryology*, 5th ed. London: Williams and Wilkins, 1985: 290–1.
9. Rickles NW, Little JW. The histogenesis of the branchial cyst. II. A study of the lining epithelium. *Am J Pathol* 1967; **50**: 765–73.
10. Work WP. Cysts and congenital lesions of the parotid gland. *Otolaryngol Clin North Am* 1977; **10**: 339–43.
11. Aronsohn RS, Batsakis JG, Rice DH, Work WP. Anomalies of the first branchial cleft. *Arch Otolaryngol* 1976; **102**: 737–40.
12. Hamilton WJ, Bond JD, Mossman HN. *Human Embryology. Prenatal Development of Form and Function*, 4th ed. Cambridge: Heffer, 1972: 131, 197, 219–20.
13. Meyer HW. Congenital cysts and fistulae of the neck. *Ann Surg* 1932; **95**: 1–26, 226–248.
14. Wengelowski R. Ueber die Halsfisteln und Cysten. *Arch Klin Chir* 1913; **100**: 789–892.
15. Bhaskar SN, Bernier JL. Histogenesis of branchial cysts. A report of 468 cases. *Am J Pathol* 1959; **35**: 407–14.
16. King ESJ. The lateral lymphoepithelial cyst of the neck. *Aust NZ J Surg* 1949; **19**: 109–21.
17. Bernier JL, Bhaskar SN. Lymphoepithelial lesions of salivary glands: classification and histogenesis. *Cancer* 1958; **11**: 1156–79.
18. Little JW, Rickles NH. The histogenesis of the branchial cyst. *Am J Pathol* 1967; **50**: 533–43.

Paper accepted 7 February 1988

Br. J. Surg. 1988, Vol. 75, August,
820–823

Bilateral spontaneous descent of the testis after the age of 10: subsequent effects on fertility

T. Bremholm Rasmussen,
H. J. Ingerslev and
H. Høstrup

Department of Surgery, Århus County Hospital, and Department of Surgery, Randers Central Hospital, Denmark
Correspondence to:
Dr T. Bremholm Rasmussen,
Department of Surgery L, Århus
Kommunehospital, DK-8000 Århus C,
Denmark

Fertility after late spontaneous descent of the testes in 45 men with previous bilateral undescended testes was evaluated on the basis of seminal analysis and concentrations of follicle-stimulating hormone (FSH) in serum. Only 15 (33 per cent) were found to have a normal fertility as estimated from the results of the total semen analysis, whereas 21 (47 per cent) were classified as being sterile or having severely reduced fertility. Elevated serum FSH concentrations in the majority of men with subnormal sperm densities supported the results of the semen analysis, indicating impaired spermatogenesis. These findings suggest that the expectant attitude in the treatment of cryptorchidism does not seem to be justified in terms of fertility and combined with recent histomorphological studies favour a more active and early treatment of undescended testes.

Keywords: Undescended testis, spontaneous descent of the testis, fertility

During the last decade, the attitude to treatment of boys with undescended testes has gradually changed towards a more active intervention at an earlier stage. At the most recent international symposia on this subject treatment has been recommended before the second year of life[1,2]. This change of attitude is chiefly based on recent histomorphological studies[3,4], which have shown that the majority of cryptorchid testes have a normal density of germ cells until the second year of life.

In Scandinavia the prevalent attitude among surgeons has been conservative, deferring treatment until prepuberty. This strategy has been based partly on the poor results as regards fertility after operative treatment, and partly on the relatively high incidence of late spontaneous descent of the testis[5].

However, the justification of an expectant policy seems rather doubtful since no controlled investigations are available concerning fertility after late spontaneous descent. On the other hand, some hesitation prevails towards the advisability of early treatment. Therefore, we considered it important to investigate the fertility of men with late spontaneous descent of the testes.

Patients and methods

The present series comprises 545 boys, referred consecutively to Århus County Hospital with undescended testes during 1967–72. From first presentation until operation, spontaneous descent or puberty, all were examined annually by the same three consultants, who had a special interest in this subject[5]. From this basic series all patients fulfilling the following criteria were selected:

(1) bilateral cryptorchidism at the time of referral;
(2) bilateral spontaneous descent at or after the age of 10, and
(3) present age of 18 or above.

The position of the testes at first presentation was defined as follows.

Type I

The testis was situated at the superficial inguinal ring or in the superficial inguinal pouch and could be manipulated to the scrotal neck, but retracted immediately.

Type II

The testis was located suprascrotally, but could be manipulated into the scrotum allowing the investigator's thumb and index finger to meet above the testis, but the testis would not remain in the scrotum.

Of the 91 men who fulfilled the criteria stipulated, 45 agreed to take part in the investigation 'study group'. Of the remaining 46 men, 28 answered a questionnaire concerning present paternity status and intercurrent diseases with potential effect on fertility; they constitute the 'questionnaire group'. Eighteen patients were lost to follow-up.

On the basis of the above definitions of testicular position the 45 men in the study group were divided into three subgroups: group I (11 with previous cryptorchidism of type I); group II (24 with previous cryptorchidism of type II); and group III (10 with a combination of type I on one side and type II on the other side).

At referral the median age was 8 years (range 2–14 years) in the study group and 7½ years (range 1½–12 years) in the questionnaire group. The median age for spontaneous descent of the latest descended testis was 12 years (range 10–16 years) in all three groups. Descent was defined as attainment of a spontaneously stable position of the testis at the bottom of the scrotum.

For each patient in the study group the investigation included a history concerning paternity status and intercurrent diseases of potential influence on fertility, a clinical examination recording position and volume of the testis using Prader's orchidometer[6], and semen analysis performed on fresh masturbatory ejaculate after 3–4 days abstinence, essentially as described by Eliasson[7]. In the case of an abnormal analysis a second sample was investigated, when possible, and the best of the two results was used in the final fertility evaluation. Each parameter of the semen analysis (sperm concentration, percentage of motile spermatozoa, degree of progressive motility and sperm morphology) was assigned a value in arbitrary units (*Table 1*).

Subsequently a 'fertility index' was calculated for each patient by multiplication of the four values obtained. Thus four classes of fertility were assigned to the following index ranges:

I Sterile (fertility index = 0)
II Severely reduced fertility (fertility index = 1–12)
III Slightly reduced fertility (fertility index = 13–24)
IV Normal fertility (fertility index = 25–36).

Finally the concentration of follicle-stimulating (FSH) in serum was determined by a commercially available kit (Amerlex Ria-Kit IM 2071, Amersham, Copenhagen, Denmark).

Results

History

Of the 45 men in the study group 38 had no knowledge of their fertility as they had made no attempt to father a child. Two had one child each and one had two children. All three had normal spermiograms/fertility class IV. One man with oligospermia (0·3 million/ml) and classified in fertility class II was stated to have fathered one aborted fetus. Three had an infertility problem of 18–24 months duration; of these one had azoospermia/fertility class I and two had oligospermia/fertility class II. Diseases of potential influence on fertility were registered in five cases. Two

Table 1 *The four parameters of seminal analysis transcribed to arbitrary units for calculation of the fertility index*

Concentration of spermatozoa		Percentage motile spermatozoa		Progressive motility		Morphology	
Millions/ml	Arbitrary unit	%	Arbitrary unit	Grade	Arbitrary unit	% Normal	Arbitrary unit
0	0	0	0	0	0	0	0
0–10	1	0–25	1	1	1	0–49	1
>10–<20	2	>25–<50	2	2	2	≥50	2
≥20	3	≥50	3	3	2		

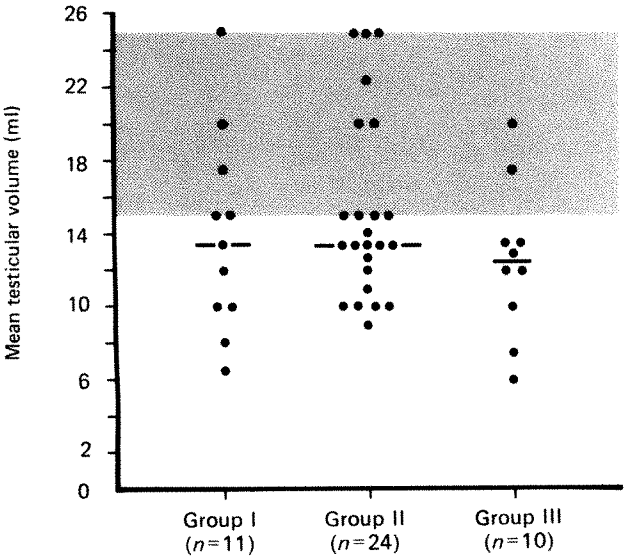


Figure 1 *Mean testicular volume calculated as the mean value of the two testes' volumes. The normal range according to Prader*[6] *is shaded. The median values for the three groups were 13·5 ml (6·5–25); 13·5 ml (9–25) and 12·5 ml (6–20)*

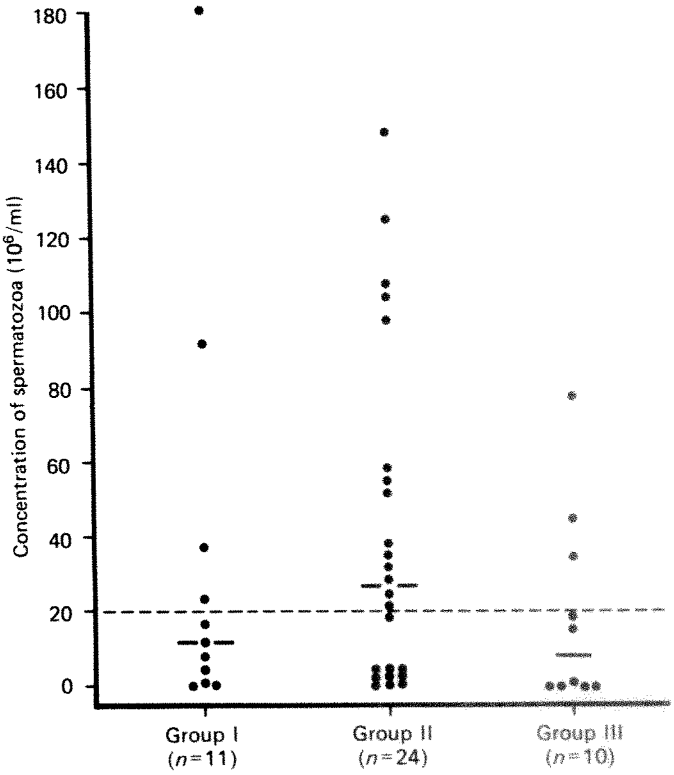


Figure 2 *The concentration of spermatozoa in millions/ml. Dotted line: lower limit of the normal range. The median values for the three groups were 12 million/ml (0–181), 27 million/ml (0·1–148) and 8 million/ml (0–78)*

of these patients had had non-specific urethritis and one uncomplicated gonorrhoea; all three had normal semen analysis/fertility class IV. One patient had had parotitis with unilateral orchitis at the age of 18 and another had had unilateral orchidectomy performed at 16 years of age due to torsion of the testis. Both had oligospermia/fertility class II.

Of the 28 men in the questionnaire group, 3 had one child each, 2 were infertile for 2 and 5 years respectively, while 23 had no knowledge of their fertility. In this group one reported intercurrent orchitis in connection with parotitis and another had had uncomplicated gonorrhoea; both were ignorant of their fertility.

The median age of the study group was 23 years (range 18–34 years) and in the questionnaire group it was 24 years (range 20–27 years). Thus no selection could be demonstrated in the study group as regards fertility status, intercurrent disease or age.

Clinical examination

All testes were spontaneously located at the bottom of the scrotum. Two patients had a left-sided varicocele. The volume of the testes was subnormal or greatly reduced in the majority of cases without significant differences between the median values for the three groups (Mann–Whitney *U* test, $P>0{\cdot}05$) (*Figure 1*).

Semen analysis

The sperm concentration was below the lower limit of the normal range (20 million/ml) for the majority of men in group I (7/11) and in group III (7/10) and for 10 of the 24 men in group II (*Figure 2*). There was no significant difference between the groups with regard to this distribution (Fisher's exact test, $P>0{\cdot}05$). The median values for sperm concentration in the three groups were not significantly different (Mann–Whitney *U* test, $P>0{\cdot}05$). An evaluation of fertility by means of the fertility index revealed the same tendency (*Figure 3*). Only a minority of men in the three groups fulfilled prevailing criteria for normal fertility, while 7 out of 11 in group I and 9 out of 24 in group II were either classified as sterile or had severely reduced fertility.

Serum FSH concentrations

These were above normal for most of the men in group I and III (7/11 and 7/10 respectively), while half of the men in group II had elevated values (*Figure 4*). There was no significant difference between the median values of FSH in the three groups (Mann–Whitney *U* test, $P>0{\cdot}05$).

The association between serum FSH concentration and sperm density showed that men with sperm counts below the normal range had significantly greater FSH levels than those with normal sperm densities (Mann–Whitney *U* test, $P<0{\cdot}05$) (*Figure 5*).

Discussion

Several classifications of the undescended testis according to its anatomical position have been proposed, but none are

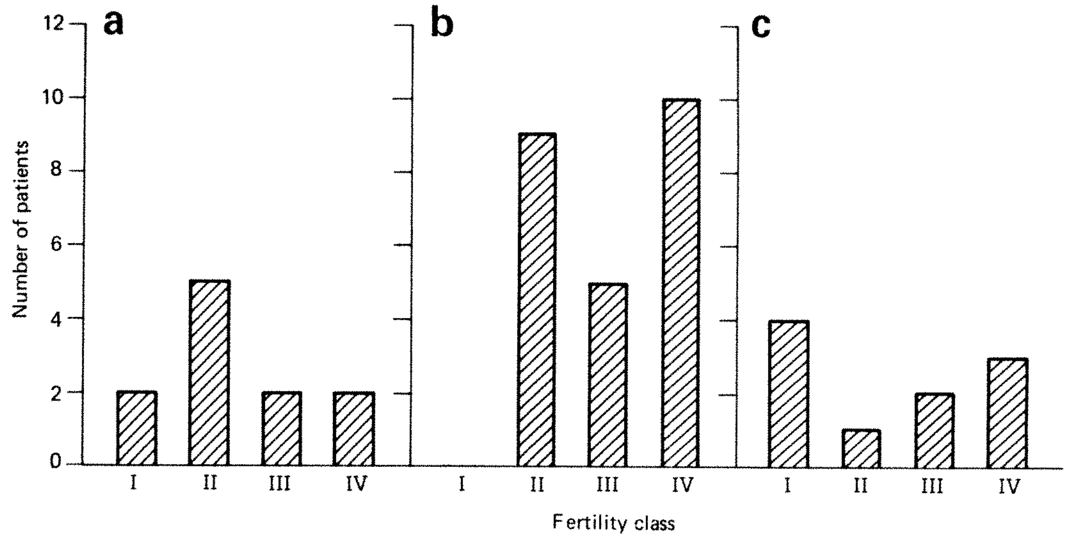


Figure 3 *Fertility class calculated on the basis of the fertility index* (Table 1) *for the three groups:* **a** *group I* (n = *11*); **b** *group II* (n = *24*); **c** *group III* (n = *10*). *I, sterile; II, severely reduced fertility; III, slightly reduced fertility; IV, normal fertility*

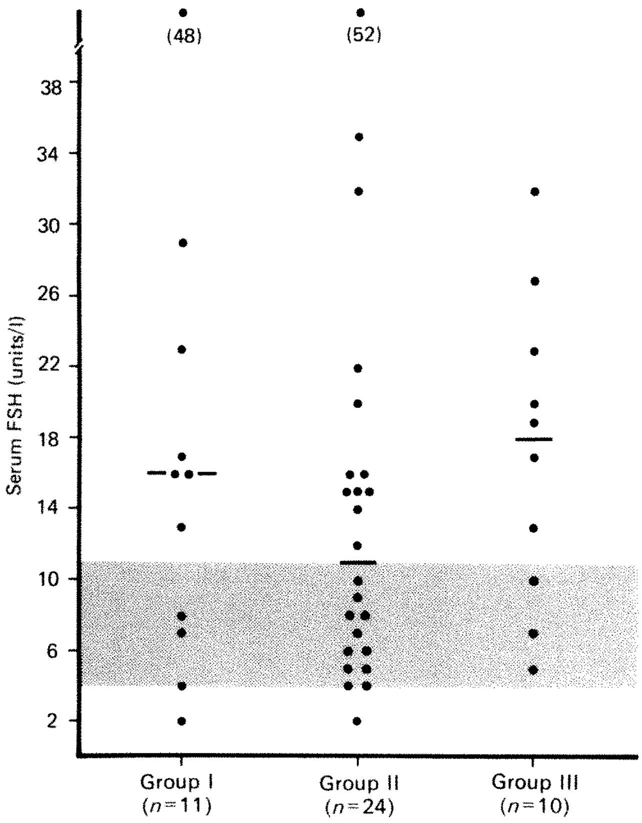


Figure 4 *Serum FSH concentrations. The shaded area shows the normal range. Median values in the three groups were 16 units/l (2–48); 11 units/l (2–52) and 18 units/l (5–32)*

universally accepted. The lack of objective definitions hampers this field of clinical research. Furthermore, previous investigators have demonstrated a considerable uncertainty at classifying testicular position on clinical palpation[5,8].

In the present investigation we have used a simple concept. The two types of testicular undescent were characterized by repeated observations of suprascrotally situated testes, which could be manipulated to a greater or lesser extent down into the scrotum, but at the termination of the manipulation the testes reassumed their suprascrotal position. It is possible that some investigators may classify the present type II as a high retractile testis. It has even been argued that all testes capable of late spontaneous descent should be classfied as retractile testes[9].

The occurrence of spontaneous descent after the age of 1 year is a controversial subject. The observations by Scorer[10] are often cited against the existence of such a phenomenon. However, Scorer excluded cases with high scrotal position from his definition of undescended testes and further changes in such cases were not registered. It is our impression that the lower the position at diagnosis the higher the chance of spontaneous descent. In our basic series of 545 boys[5] spontaneous descent was observed during the observation period at all ages up to puberty in 20 per cent of type I cases and in 57 per cent classified as type II. Accordingly, we would assume that the lack of spontaneous descent in Scorer's series is at least partially due to exclusion of the lowest positioned testes with the highest chance of spontaneous descent. However, it may be argued that the low situated testes are just normal variants, which should not be treated. The present study speaks strongly against such a concept, since not only men with previous type I, but also those with type II, testes were found to have a high risk of later impaired sperm production. Of the 45 men only 15 had normal semen analysis, whereas 21 were classified as being sterile or having severely reduced fertility as estimated from the results of the total semen analysis. Based on sperm counts alone, 18 had severely impaired fertility with counts less than 5 million/ml. It is known that repeated semen analysis from the same individuals may show a considerable variation[7] and a certain margin of error exists in the analysis. In 21 out of 30 men with subnormal fertility it was possible to repeat the semen analysis and in no case did the second sample show a normal result, but fertility index improved one class in four men, decreased one class in two and was unchanged in the remaining. In addition the high levels of FSH in serum from the majority of men with subnormal sperm densities support the results of the semen analysis, indicating impaired spermatogenesis[11–13].

The present results show that spontaneous descent of bilateral undescended testes after the age of 10 carries a serious risk of later impaired spermiogenesis. The fact that even low positioned testes may be damaged indicates that deficient testicular descent at all stages should be considered as one disease with a clinical spectrum ranging from abdominal to high scrotally situated testes. Retractile testes, on the other hand, are generally accepted as normal variants needing no treatment, as normal fertility can be expected in the adult. The study by Puri and Nixon[14], mainly based on questionnaire interviews, has been widely cited in support of this concept. However, recent studies by Nistal and Paniagua[15] and Abyholm *et al.*[16] have

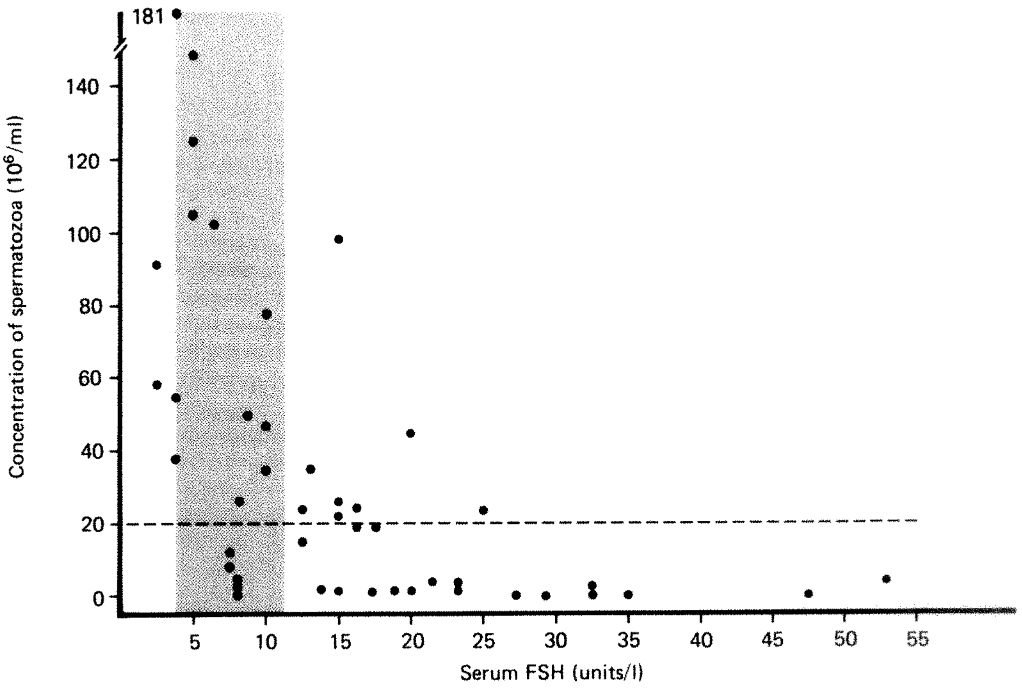


Figure 5 *The concentration of spermatozoa in relation to serum FSH concentration in 45 men. The shaded area shows the normal range of FSH. The dotted line indicates the lower limit of normal range for the sperm concentration*

demonstrated that even testicular retractility can be associated with impaired fertility. Accordingly, only testes, which by gentle manipulation can be coaxed to the bottom of the scrotum under favourable conditions, should be classified as retractile testes, probably requiring no treatment.

On the basis of the present investigation and recent histomorphological studies[3,4] it is difficult to maintain an expectant, conservative attitude in the treatment of undescended testes.

References

1. Backhouse KM, Bierich JR, Hadziselimović F *et al.* Panel discussion. SUWO, Rotterdam 1982. *Eur J Pediatr* 1982; **139**: 292–4.
2. Sixth Congress of the European Association of Urology. Session 1: The undescended testis. Copenhagen 1984.
3. Hedinger C. Histological data in cryptorchidism. In: Job JC. *Cryptorchidism, Diagnosis and Treatment.* Basel: Karger, 1979: 3–13.
4. Hadziselimović F. Pathogenesis and treatment of undescended teeste. *Eur J Pediatr* 1982; **139**: 255–65.
5. Høstrup H, Linnet-Jepsen P, Franch P. Undescended testes. Subdivision and development. *Ugeskr Laeger* 1978; **140**: 1743–8.
6. Prader A. Testicular size. Assessment and clinical importance. *Triangle* 1966; **7**: 240–3.
7. Laboratory manual for the examination of human semen and semen-cervical mucus interaction. Genève: WHO, 1980.
8. Cour-Palais JJ. Spontaneous descient of the testicle. *Lancet* 1966; **i**: 1403–5.
9. Lipschultz LI. Cryptoorchidism in the subfertile male. *Fertil Steril* 1976; **27**: 609–20.
10. Scorer CG. The descent of the testis. *Arch Dis Child* 1964; **39**: 605–9.
11. Johnsen SG. The stage of spermatogenesis involved in the testicular-hypophyseal feed-back mechanism in men. *Acta Endocrinol* 1970; **64**: 193–210.
12. Kjessler B, Wide L. Follicle stimulating hormone (FSH) and interstitial cell stimulating hormone (ICSH) in relation to gametic output in 643 males. *Acta Endocrinol* 1973; **72**: 245–56.
13. Bramble FJ, Houghton AL, Eccles JS, Murray MAF, Jacobs HS. Specific control of follicle stimulating hormone in the male: postulated site of action of inhibin. *Clin Endocrinol* 1975; **4**: 443–9.
14. Puri P, Nixon HH. Bilateral retractile testes—subsequent effects on fertility. *J Pediatr Surg* 1977; **12**: 563–6.
15. Nistal M, Paniagua R. Infertility in adult males with retractile testes. *Fertil Steril* 1984; **41**: 395–403.
16. Abyholm T, Øian P, Gordeladze JO. True cryptorchidism and retractile testes in infertile men. *Acta Eur Fertil* 1986; **17**: 15–18.

Paper accepted 26 February 1988

Br. J. Surg. 1988, Vol. 75, August, 824–826

Penetrating injuries of the diaphragm

D. Demetriades, S. Kakoyiannis, D. Parekh and C. Hatzitheofilou

*Department of Surgery,
Baragwanath Hospital and
University of the Witwatersrand,
Medical School, York Road,
Parktown 2193, Johannesburg,
South Africa
Correspondence to:*
Dr D. Demetriades

This study involved 163 patients with penetrating injuries of the diaphragm (knife, 139; bullet, 24). Intra-abdominal injuries were present in 122 patients (75 per cent) and this resulted in early diagnosis and treatment of the associated diaphragmatic injury (mortality 3·2 per cent). In the remaining 41 patients (25 per cent) the injury was confined to the diaphragm, and the diagnosis was missed during the initial admission in 10 patients who returned at a later stage with diaphragmatic hernia. A diaphragmatic hernia was found in 24 cases (14·7 per cent). Fourteen of these were diagnosed during the initial admission (mortality 7·1 per cent) and the remaining ten were diagnosed during a subsequent admission (mortality 30 per cent). The initial chest radiograph was diagnostic of diaphragmatic injury in 13 per cent, abnormal but not diagnostic in 76 per cent, and completely normal in 11 per cent. The importance of early diagnosis in reducing mortality, morbidity and hospital stay is emphasized. A high index of suspicion, careful clinical examination, and serial chest radiographs remain the best way of making the diagnosis.

Keywords: Diaphragmatic injuries, diagnostic problems

Penetrating wounds of the chest or abdomen are often associated with diaphragmatic injuries, which are commonly missed, because of lack of clinical suspicion, absence of distinct symptoms, and absence of diagnostic radiological signs. In this study we have reviewed our experience with this type of trauma. Blunt trauma was not included because of different pathogenesis, diagnostic problems and prognosis.

Patients

This is a review of 163 patients with penetrating injuries of the diaphragm, treated at Baragwanath Hospital, Johannesburg, during a 3½-year period (January 1984–July 1987). Most of the patients were male (94 per cent), and their ages ranged from 14 to 64 years (mean 25 years). The injury was inflicted by a knife in 139 patients (85 per cent) and by a bullet in 24 patients (15 per cent).

Results

Entrance wounds

In all patients with knife injuries the wound was located below the level of the nipples. In bullet injuries no correlation was found between the site of the entrance wound and the presence of a diaphragmatic injury.

Clinical presentation

In 139 patients without a hernia there were signs of an acute abdomen on admission. At operation 120 patients had associated intra-abdominal injuries and 19 patients had isolated diaphragmatic injuries. In the patients with a diaphragmatic hernia 19 had upper abdominal pain, 7 had cardiorespiratory distress, 5 had intestinal obstruction and 2 had an acute abdomen. However, 10 of these patients were asymptomatic during the initial admission.

Radiological findings

In 20 patients no films were available. In the remaining 143 patients the chest radiographs or the radiological reports were traced. Overall, the initial films were diagnostic of diaphragmatic injury (e.g. viscus in the chest, elevated diaphragm) in 13 per cent of the patients, abnormal but not diagnostic (e.g. haemothorax, pneumothorax, obscured diaphragmatic shadows) in 76 per cent and normal in 11 per cent. The diagnostic accuracy of the chest radiograph in patients with hollow viscus herniation into the chest was 74 per cent, but in those with uncomplicated diaphragmatic injuries this figure was only 6 per cent. Contrast studies of the gastrointestinal tract were 100 per cent diagnostic in patients with hollow viscus herniation.

Operative findings

The left diaphragm was injured in 123 cases (75 per cent), the right diaphragm in 37 cases (23 per cent), and both diaphragms in 3 cases (2 per cent). In the majority of patients ($n = 122$ or 75 per cent) there were associated injuries requiring repair. The most commonly injured structures were the stomach (50 cases), followed by the liver (48 cases), the spleen (23 cases), the colon (22 cases), the kidneys (10 cases), the small bowel (8 cases), and the pancreas (3 cases). In the 24 patients with diaphragmatic hernia the most commonly herniating viscera were the colon, the stomach, and the omentum (nine cases) followed by the small bowel (four cases), and the spleen (one case). In early hernias the sac contained an average of one viscus, compared with more than two viscera in late hernias.

Mortality, morbidity and hospital stay

The overall mortality was 4·9 per cent. In the group of 139 patients with diaphragmatic injury but no hernia there were four deaths (2·9 per cent), as compared with four deaths (16·7 per cent) in the group of 24 patients with diaphragmatic hernia (χ^2 test, $P < 0{\cdot}05$). In all deaths in the group of patients with hernia the colon was a herniating viscus (*Table 1*). When the diagnosis of a diaphragmatic hernia was made during the initial admission, the mortality was 7·1 per cent compared with 30 per cent for delayed diagnosis. Overall, 14·5 per cent of the patients developed complications. Atelectasis not prolonging hospital stay was not included. The most common complication was pneumonia (6 per cent of patients), followed by wound sepsis (5·6 per cent), empyema (4·6 per cent), and subphrenic abscess (1·3 per cent). The incidence of complications in patients with early diaphragmatic hernia was 35·7 per cent and in

0007–1323/88/080824–03$3.00

Table 1 *Mortality in patients with diaphragmatic hernia*

Patients	Time of diagnosis	Herniating viscus	Cause of death	Comments
1	Early	Colon	Sepsis	Gangrenous colon
2	Late	Colon, stomach, small bowel	Respiratory failure	Admitted with respiratory failure
3	Late	Colon	Sepsis	Gangrenous colon
4	Late	Colon	Sepsis, respiratory failure	

Table 2 *Results in 163 patients with diaphragmatic injuries*

Patients	*n*	Mortality (%)	Morbidity (%)	Hospital stay (days)
Without diaphragmatic hernia	139	2·9	12·6	6
With early diaphragmatic hernia	14	7·1	35·7	11·6
With late diaphragmatic hernia	10	30	60	29

patients with late hernia 60 per cent, compared with 12·6 per cent in patients without a hernia (*Table 2*). The mean hospital stay for patients with uncomplicated diaphragmatic injuries was 6 days, for those with early diaphragmatic hernias 11·6 days, and for those with late hernias 29 days (*Table 2*).

Discussion

The results of this study emphasize the importance of early diagnosis and repair of injuries of the left diaphragm. Delayed diagnosis resulted in increased mortality, morbidity and a longer hospital stay.

In most penetrating diaphragmatic injuries there are associated intra-abdominal injuries. Such patients are operated on for an acute abdomen, and the diagnosis of diaphragmatic injury is made intra-operatively. It is important that at laparotomy the diaphragm is checked, especially after knife injuries involving the lower chest or the upper abdomen. This step can easily be forgotten by the inexperienced trauma surgeon.

In patients with isolated diaphragmatic injuries the diagnosis may be difficult: they often present as an acute abdomen; alternatively they may present with signs of a diaphragmatic hernia, i.e. bowel obstruction and cardiorespiratory distress. However, many patients have no clinical signs after the initial injury. The diagnosis may thus be missed, unless the radiological investigations demonstrate the lesion.

Various investigations have been used for the diagnosis of diaphragmatic injury. The simplest and most useful investigation is a chest radiograph, which was diagnostic in 13 per cent of our cases and abnormal but not diagnostic in 76 per cent. In about 10 per cent of cases the initial chest radiograph was completely normal. Diagnostic radiological signs are an elevated diaphragm and the presence of a hollow viscus in the chest. Some other radiological findings should be regarded as suspicious and further investigations should be carried out to exclude diaphragmatic injury: these radiological signs include an irregular or obscured diaphragmatic shadow, an encysted basal pneumothorax, air fluid levels in the basal left lung fields, and the combination of a pneumothorax with free intraperitoneal air but a soft abdomen. The diagnostic accuracy of the chest radiograph may be increased by inserting a nasogastric tube with a radio-opaque tip, when a herniated stomach is suspected.

Many other investigations have been used for the diagnosis of diaphragmatic injuries. In suspected diaphragmatic hernias, radiographic contrast studies of the gastrointestinal tract, ultrasonography[1] and CAT scanning[2] are very useful. In uncomplicated diaphragmatic perforations the radiological diagnosis is more difficult. Thoracoscopy, if performed within 24 h of the injury before the formation of adhesions, may be helpful[2]. Diagnostic pneumoperitoneum has also been used with limited success; it may interfere with subsequent abdominal examinations, and it may be falsely negative, if the tear is sealed by a herniating viscus.

Diagnostic peritoneal lavage has been used for the early diagnosis of diaphragmatic injuries, but with disappointing results. Freeman and Fischer[3] reported an incidence of 25 per cent and Miller *et al.*[4] an incidence of 20 per cent of falsely negative lavages. Sealing of the perforation by an abdominal viscus may control bleeding or divert the blood into the thoracic cavity; in addition, the negative intra-thoracic pressure sucks the blood into the chest.

The natural history of unrepaired diaphragmatic injuries is not known. Most penetrating diaphragmatic tears are less than 2 cm long[5]. Herniation may occur during the early or late stages. The pressure gradient between the abdominal and thoracic cavity may enlarge the defect and progressive herniation may take place[2]. It is possible that the majority of missed diaphragmatic injuries heal without problems. During the $3\frac{1}{2}$-year period that we reviewed, we recorded only 10 cases of late diaphragmatic hernias after knife wounds. During the same period we treated more than 7000 patients with penetrating injuries of the chest. In managing thoracic injuries we follow a very conservative non-operative approach. However, because of the high mortality and morbidity of late diaphragmatic hernias, every effort should be made to diagnose and repair any diaphragmatic injury. We do not agree with the suggestion made by Miller *et al.*[4] that all patients with abdominal or lower thoracic penetrating injuries should have exploratory laparotomy. Mandatory exploration is associated with an unacceptably high incidence of negative laparotomies, in some series up to 50 per cent[6,7]. Our policy is one of selective conservatism, for both thoracic and abdominal penetrating injuries[8,9]. In most patients with diaphragmatic injuries there is an associated intra-abdominal injury and the diagnosis is made at laparotomy. For patients with isolated diaphragmatic injuries the diagnosis should be based on the triad of a high index of suspicion, a good physical examination and serial chest radiographs.

References

1. Amman A, Brewer W, Mauli K. Traumatic rupture of the diaphragm: real time sonographic diagnosis. *AJR* 1983; **140**: 915–16.
2. Adamthwaite D. Traumatic diaphragmatic hernia. *Surg Annu* 1983; **15**: 73–97.
3. Freeman T, Fischer R. The inadequacy of peritoneal lavage in diagnosing acute diaphragmatic rupture. *J Trauma* 1976; **16**: 538–42.

4. Miller L, Bennet E, Root D, Trinkle K, Grover F. Management of penetrating and blunt diaphragmatic injury. *J Trauma* 1984; **24**: 403–9.
5. Wise L, Connors J, Hwang Y, Anderson C. Traumatic injuries to the diaphragm. *J Trauma* 1973; **13**: 945–50.
6. Forde K, Ganepola G. Is mandatory exploration for penetrating abdominal trauma extinct? The morbidity and mortality of negative exploration in a large municipal hospital. *J Trauma* 1974; **14**: 764–6.
7. Maynard A, Oropeza G. Mandatory operation for penetrating wounds of the abdomen. *Am J Surg* 1968; **115**: 307–12.
8. Demetriades D, Rabinowitz B, Markides N. Indications for thoracotomy in stab injuries of the chest: a prospective study of 543 patients. *Br J Surg* 1986; **73**: 888–90.
9. Demetriades D, Rabinowitz B. Indications for operation in abdominal stab wounds. A prospective study of 651 patients. *Ann Surg* 1987; **305**: 129–32.

Paper accepted 29 February 1988

Case report

Br. J. Surg. 1988, Vol. 75, August, 826

A serious complication of the Angelchik prosthesis

N. R. Boeree, C. P. Armstrong, C. Brown and B. Pickering

Department of Surgery, Derriford Hospital, Plymouth, Devon PL6 8DH, UK

Correspondence to: Dr N. Boeree

The Angelchik antireflux prosthesis was first introduced in 1973, and since that time has gained popular acceptance in the surgical treatment of gastro-oesophageal reflux. There are accumulating in the literature, however, a sufficient number of reports of serious complications arising from the use of the Angelchik antireflux prosthesis to cause concern.

Case report

In January 1985, a 60-year-old woman presented with a 10-year history of reflux oesophagitis and a benign lower oesophageal stricture which had become unresponsive to medical treatment and repeated dilatations. She underwent routine insertion of an Angelchik antireflux prosthesis, and a postoperative radiograph showed the prosthesis to be in the normal position. The patient made a good postoperative recovery and remained completely symptom free for 16 months. At this stage she developed progressive dysphagia, and a barium meal demonstrated that the prosthesis had migrated into the chest and was lying in a vertical plane causing obstruction (*Figure 1*). In view of the patient's severe symptoms, it was decided to remove the prosthesis and to perform an oesophageal dilatation.

At laparotomy the prosthesis was not palpable in the posterior mediastinum via the hiatus. Oesophagoscopy showed that at least part of the prosthesis was intraluminal and consequently an Ivor–Lewis oesophagogastrectomy was performed. The patient made a good recovery and was discharged 2 weeks after surgery.

Figure 2 demonstrates the excised specimen of oesophagus and stomach. This has been opened to show the dense fibrosis surrounding the prosthesis which can be clearly seen to lie entirely within the lumen, although the Prolene (Ethicon Ltd., UK) knot is extraluminal.

Discussion

The Angelchik prosthesis has been used extensively in the treatment of reflux oesophagitis. Reports concerning its efficacy are varied, but appear to compare favourably with the other operative procedures that are currently employed[1–3]. Studies have reported relief in up to 96 per cent of those treated[1–4]. A recent comprehensive survey[5] demonstrated the complications that have been encountered in the United Kingdom, and showed a complication rate of 9 per cent, with 5 per cent of prostheses requiring subsequent removal. This is supported by previous reports[2,3]. The survey by Morris *et al.*[5] revealed that migration and erosion are among the commonest problems necessitating removal of the Angelchik prosthesis. It should be noted, however, that migration into the chest may be asymptomatic and need not necessarily interfere with the function of a prosthesis[6].

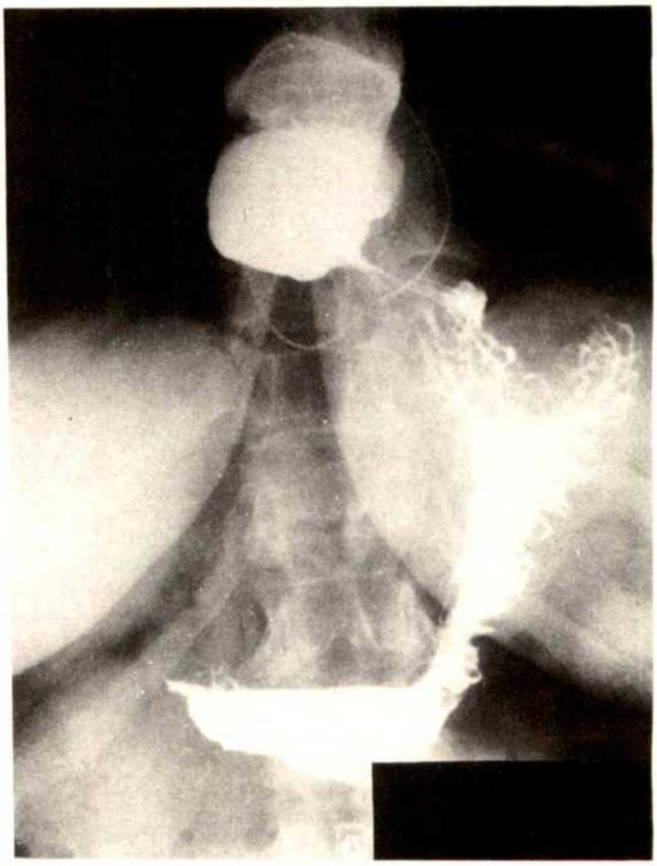


Figure 1 *Barium meal showing prosthesis within the chest, lying in a vertical plane causing obstruction*

Erosion is usually a delayed complication and may occur many months or even years after the original operation. Interestingly, there have been no reports of free perforation

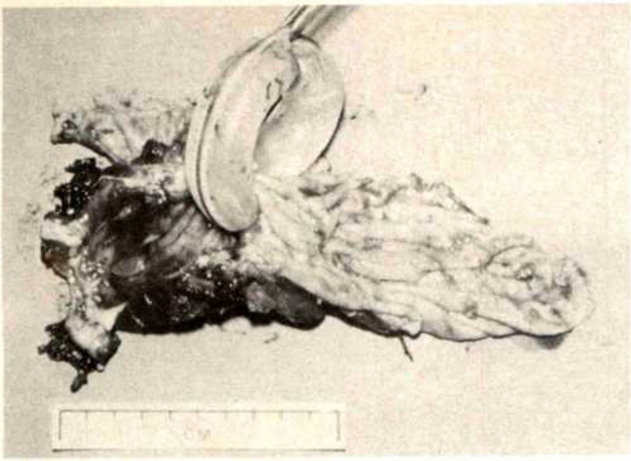


Figure 2 *The opened specimen of oesophagus, showing the prosthesis lying within the lumen, except for the Prolene knot*

resulting from erosion, and the condition may, on occasion, cause only minor symptoms. There has been considerable speculation concerning the mechanism of erosion. The manufacturers recommend that, should the bowel lumen be opened either deliberately or inadvertently, the prosthesis should not be used. Of the described cases of erosions, several have occurred at or near the site of a previous oesophagogastric anastomosis or else insertion of the prosthesis has been combined with another procedure such as cholecystectomy or vagotomy and pyloroplasty[6,7]. Sepsis may be important, with drainage of pus into the adjacent gut lumen providing a means of erosion of the prosthesis into the stomach or oesophagus[4]. Others have implicated the knot in the Dacron ties.

The case that we have described demonstrates that erosion may occur in the absence of any of these proposed aetiological factors. Excellent symptomatic relief was obtained for over 16 months making it unlikely that erosion was due to sepsis or poor technique. The possible erosive nature of the knot is repudiated by this case in which the entire prosthesis *except* the knot had become intraluminal.

It should be stressed that, in most cases, the Angelchik prosthesis may be easily removed. Gastro-oesophagectomy, although indicated only rarely, none the less carries with it serious hazards for the patient. Caution should be exercised until more is known about the long-term safety of the prosthesis, and the delayed nature of complications should be borne in mind in patients who have received an Angelchik prosthesis who present with new gastrointestinal symptoms.

Acknowledgements

Our thanks are due to the Medical Photography Department, and also to Mrs A. Toms for kindly producing the transcript.

References

1. Angelchik JP, Cohen R. A new surgical procedure for the treatment of gastro-oesophageal reflux. *Surg Gynecol Obstet* 1979; **148**: 246–8.
2. Wale RJ, Royston CMS, Bennett JR, Buckton GD. Prospective study of the Angelchik anti-reflux prosthesis. *Br J Surg* 1985; **72**: 520–4.
3. Durrans D, Armstrong CP, Taylor TV. The Angelchik anti-reflux prosthesis—some reservations. *Br J Surg* 1985; **72**: 525–7.
4. Gear MWL, Gillison EN, Dowling BL. Randomized prospective trial of Angelchik anti-reflux prosthesis. *Br J Surg* 1984; **11**: 681–3.
5. Morris DL, Robertson CS, Hardcastle JD. National survey of use of the Angelchik anti-reflux prosthesis. *Br Med J* 1987; **295**: 308–9.
6. Lilly MP, Slaksky F, Thomson W. Intra luminal erosion and migration of the Angelchik prosthesis. *Arch Surg* 1984; **119**: 849–53.
7. Lackey C, Potts J. Penetration into the stomach—a complication of the Angelchik prosthesis. *JAMA* 1982; **248**: 350.

Paper accepted 17 January 1988

BJS
75

Correspondence

Colorectal cancer in the elderly

Sir

I read with interest the paper by Mr T. T. Irvin on 'Prognosis of colorectal cancer in the elderly' (*Br J Surg* 1988; **75**: 419–21).

The major difference between this study and the study which was reported from Birmingham in 1986 is in the incidence of emergency presentation of the disease, both in the under 70 and in the over 70 age group. In the Birmingham series, 58 per cent of the elderly patients were admitted as an emergency and 43 per cent of the younger age group; whereas, in Mr Irvin's study corresponding figures are 18 and 11 per cent. It was the high incidence of emergency presentation and its serious consequences, particularly in the elderly, which was highlighted in the Birmingham paper. The authors did not suggest that the pathology of tumours in the elderly was unfavourable *per se*, as was suggested in the discussion in Mr Irvin's paper, but that the staging in both emergency groups, whether over or under 70, was unfavourable in comparison with the elective cases as approximately 30 per cent of all emergencies were stage 'D'. Disseminated disease was the cause of death in one quarter of the deaths in the emergency groups. The vast majority of the remainder were due to cardio-respiratory complications, and indeed severe pre-existing disease other than malignancy was considered to render the patients unfit in 11 per cent of the emergencies over the age of 70 compared with only 2 per cent under the age of 70.

I would agree with Mr Irvin's comments that differences in public awareness and standards of primary care are probably very important in influencing the timing of presentation of this disease. Dudley Road Hospital serves a predominantly poor area of inner Birmingham with many elderly people living alone. The concluding paragraph emphasized the belief that early diagnosis is very important, particularly in the elderly patients as they do especially badly if the primary disease is allowed to progress to produce obstruction or perforation. I agree with Mr Irvin that elderly patients with large bowel malignancy should be treated by surgical resection whenever possible, and should not be denied treatment that would be offered to younger patients.

I. A. Donovan

Dudley Road Hospital
Birmingham B18 7QH
UK

Extended abdominal rectopexy

Sir

A recent report by C. V. Mann and C. Hoffman (*Br J Surg* 1988; **75**: 35–7) described favourable results in the treatment of complete rectal prolapse by extended abdominal rectopexy. They concluded that lesser procedures such as perineal rectopexy, modified Thiersch's operation using a TEFLON® prosthesis and Delorme's operation were not justified except in extreme circumstances as they were almost certain to fail. However, any abdominal procedure poses considerable risk for elderly or frail patients, and following the report by Manson *et al.*[1] we have used Delorme's procedure for the treatment of five such female patients (mean age 82 years, age range 69–90 years) with complete rectal prolapse, over the past 18 months. Pre-operative symptoms included bleeding (three patients), constipation (two patients) and faecal incontinence (one patient).

The operative technique described by Manson *et al.* proved to be simple and quick. Although our patients had a general anaesthetic, the operation may be performed using local anaesthetic. There were no postoperative deaths and four patients had a good result with no residual or recurrent rectal prolapse (partial or full thickness). Two patients were faecally incontinent postoperatively, continuing for 1 month in one patient, before settling spontaneously. The other had a lax, gaping anus which continued to prolapse after the repair until a modified Thiersch operation was performed and subsequently the incontinence settled.

All five patients continue to do well at follow-up (mean 11 months). Long-term results are not available for our small number of patients but the incidence of recurrence varies from 7 per cent[1] to 17 per cent[2], 21 per cent[3] and 31 per cent[4]. Manson *et al.* made the point that many of these elderly and infirm patients do not survive long enough to develop recurrent prolapse and further recurrence may be dealt with by a repeat Delorme's procedure.

Delorme's operation offers a simple and relatively safe procedure with a good functional result for the elderly and frail patient with a full thickness rectal prolapse.

N. D. Heaton
J. A. Rennie

The Dulwich Hospital
London SE22 8PT
UK

1. Manson JRT, Jones NAG, Vowden P, Brennan TG. Delorme's operation: the first choice in complete rectal prolapse. *Ann R Coll Surg* 1986; **68**: 143–6.
2. Christiansen J, Kirkegaard P. Delorme's operation for complete rectal prolapse. *Br J Surg* 1981; **68**: 537–8.
3. Nay HR, Blair CR. Perineal surgical repair of rectal prolapse. *Am J Surg* 1972; **123**: 577–9.
4. Swinton NW, Palmer TE. The management of rectal prolapse and procidentia. *Am J Surg* 1960; **99**: 144–51.

Author's reply

Sir

I waited many years to publish the results of abdominal rectopexy in a substantial number of cases and without selection bias: the mean time of follow-up was 5 years. I hoped that by this means I would be able to convince others at least of the safety of abdominal rectopexy, whatever other merits the procedure might have. I can only repeat strongly that there is no need to prefer perineal procedures because they are 'safer'. The recurrence figures quoted by Mr Rennie and Mr Heaton vary between 7 and 31 per cent: I believe these confirm that perineal operations carry an unsatisfactory prognosis for recurrence, and that as these operations are followed up as time passes, there is an increasing tendency for failure. Repeated perineal operations will carry both a substantial morbidity and a mortality in 'elderly and infirm' patients.

I do not find a good case on the data presented for preferring perineal surgery for complete rectal prolapse unless in the most desperate and exceptional circumstances.

C. V. Mann

The London Hospital
London E1 1BB
UK

Internal jugular vein cannulation

Sir

We read with interest the refinements of technique for insertion of long term central venous cannulae suggested by Eckersley and Dudley (*Br J Surg* 1987; **74**: 1003), but note with alarm that they recommend Prolene® for the purse-string suture in the exposed internal jugular vein. For several years surgeons at the Royal Free Hospital have used a technique which is similar in most respects[1], and wish to bring to your attention a potentially serious complication which has arisen in two of our patients when Prolene was used for the purse-string in the internal jugular vein.

Case 1. A 42-year-old woman was receiving cytotoxic chemotherapy for metastatic carcinoma of the breast. After major difficulty with venous access, a Hickman catheter was inserted by direct catheterization of the exposed internal jugular vein[1] using a 5/0 Prolene purse-string suture in the vein. After 8 months of chemotherapy her disease was in remission and so the catheter was removed. Local anaesthetic was infiltrated around the fabric cuff which was mobilized, then the catheter was withdrawn. Initially slight resistance was felt, then the catheter came out only too easily. The length of catheter retrieved did not appear to be sufficient and the tip was cut more obliquely than usual. Later a chest X-ray film demonstrated an 8 cm length of catheter lying in the right pulmonary artery. Fortunately this was later retrieved using a percutaneous transvenous method.

Case 2. A 16-year-old girl with acute lymphoblastic leukaemia had a Hickman catheter inserted using a 5/0 Prolene purse-string suture. After 12 months of cytotoxic chemotherapy her disease was in remission and so the catheter was removed After mobilization of the cuff, resistance to withdrawal of the catheter was met, so the patient was anaesthetized and the neck explored The Prolene purse-string was found to have cut into the side of the catheter and then split it longitudinally for a length of 3 cm. Cutting the Prolene enabled the catheter to be withdrawn without further difficulty.

Both cases demonstrate that Prolene used as a purse-string can cut into the soft material of a Hickman catheter and in one of our patients this led to embolism of part of the catheter. Following this experience we recommend that an absorbable suture such as PDS or chromic catgut should be used for the purse-string in the internal jugular vein and that if any resistance is met when withdrawing the catheter, the neck should be explored.

H. S. Rogers
S. P. Parbhoo*

The London Hospital
London E1 1BB
UK

**Royal Free Hospital*
London NW3
UK

1. Sagor G, Mitchenere P, Layfield J, Prentice HG, Kirk RM Prolonged access to the venous system using the Hickman right atrial catheter. *Ann R Coll Surg Engl* 1983; **65**: 47–9

Cholangiography during biliary tract surgery

Sir

Now that it is generally accepted that cholangiography should be a routine intra-operative procedure during biliary tract surgery, remaining controversy is concerned with the preferred method of introducing radio-opaque contrast into the biliary tract as exemplified by the article by Williams, Patterson, Kiff and Davies (*Br J Surg* 1988; **75**: 149). Notably absent in these publications, either because of oversight or unawareness, is any reference to a method of operative cholangiography which, in my opinion, has considerable advantages over the present standard methods: this is transcholecystic operative cholangiography which is carried out by introducing contrast into the gallbladder via the fundus after evacuating its contents, and then propelling the dye from the gallbladder into the biliary tract before taking the X-ray films (Tinckler[1]).

This technique has several advantages: it is easy, rapid to perform and effective; dye is introduced into the biliary tract at its most superficially presenting part, i.e the fundus (therefore dissection into Calot's triangle in the deepest part of the operation wound is obviated); cholangiograms are obtained at an early stage of the operation, i.e. immediately after making the parietal incision (thus, radiographers are not detained in the operating theatre until the surgeon cannulates the cystic duct, which may at times prove difficult, hazardous or even impossible) There are no hazards associated with the procedure; the anatomy of the biliary tract is imaged and any anatomical anomalies are noted before any further operative steps are undertaken.

For the past 20 years, I have routinely carried out operative cholangiography by this method in over 400 patients and would consider using no other; it is facilitated by instruments specially designed for introducing radio-opaque contrast into the gallbladder (Tinckler[2]).

I cannot understand all the agonizing over the merits or otherwise of cannulating the cystic duct or puncturing the common bile duct to achieve operative cholangiography as both of these methods have faults which may be serious. In their article, Williams, Patterson, Kiff and Davies reported that 2 patients who had needle puncture of the common bile duct required reoperation for bile leakage, and attempted cannulation of the cystic duct in 9 patients out of 69 was unsuccessful (13 per cent)—a failure rate which I would regard as unacceptable in a method of cholangiography chosen for routine application. Happily, the method of operative cholangiography I use is free from these problems.

L. F. Tinckler

Wrexham Maelor Hospital
Wrexham
UK

1. Tinckler LF Techniques of operative cholangiography *J R Coll Surg Edinb* 1974; **19**: 316
2. Tinckler LT. Cannula and gall bladder holding clamp for operative cholangiography *Lancet* 1972; **ii**: 409.

Tubulovillous neoplasms of the duodenum

Sir

We were interested to read the paper by Krukowski *et al* (*Br J Surg* 1988; **75**: 150–3) describing the operative management of patients with tubulovillous neoplasms of the duodenum and wish to relate the following case.

A 36-year-old woman suffered six attacks of acute pancreatitis between April and December 1977 and was referred from another hospital for investigation. Endoscopic retrograde cholangiopancreatography was impossible due to a neoplasm around the ampulla of Vater. At operation, a 2-cm diameter, sessile lesion was found and totally excised by submucus dissection together with a short length of common bile duct. Histologically, the lesion was a tubulovillous adenoma without evidence of malignancy. The patient made a good recovery and was asymptomatic for almost 10 years. In December 1987 she suffered another attack of acute pancreatitis and subsequent endoscopy revealed a further periampullary adenoma the biopsies of which had histological appearances identical to those seen previously The patient was treated by pancreaticoduodenectomy in February this year. The operative specimen showed a 2-cm sessile polyp at the ampulla of Vater which was a typical villous adenoma with epithelial atypia but no invasion The common bile duct and pancreatic duct were free of tumour.

We agree with the principle of local excision of non-invasive duodenal villous adenomas but our case illustrates the recurrent potential of these lesions which is not mentioned by Krukowski *et al.*

We propose that patients undergoing local excision of duodenal villous adenomas should be followed up regularly by endoscopy or hypotonic duodenography to enable treatment of recurrent tumours before they become invasive.

I. M. Muir
K. C. Ballantyne
J. L. Wilkins

City Hospital
Nottingham NG5 1PB
UK

Ampullary carcinoma

Sir

We believe further comment is required on the issue of local resection *versus* Whipple's resection for ampullary carcinoma raised by Messrs Knox and Kingston (*Br J Surg* 1988, **75**: 291–2) In their original paper[1] these authors reported a 50 per cent actuarial survival rate for local resection and 25 per cent for a Whipple's resection. The apparent logic that local resection is an adequate operation does not necessarily follow for two important reasons.

Firstly, Knox and Kingston state that all their patients were followed up until death or were lost to follow-up[1]. However, their results may still be biased if there was a major discrepancy between the groups in terms of cases 'lost to follow-up' as they would statistically be treated as 'censored', i.e as survivors

Secondly, studies from Leicester would seem to indicate that the main indicators of survival are related to the stage of the disease and to the degree of differentiation[2,3]. These are independent survivor functions and may be combined into a simple scoring system (2–7). Patients with the lowest scores (2–4) had a 79 per cent 5 year survival rate, compared with 0 for those with the highest scores (5–7) Thus, if the patients who had a local resection in Manchester were in the low scoring group a survival rate of only 50 per cent would be poor.

Before embarking on a major national (or international!) trial it may be worthwhile reviewing the histology of the Manchester group of patients. It is perhaps of some significance that findings very similar to those in Leicester have recently been reported from Japan[4]. We would like to invite interested parties, including Messrs Knox and Kingston, to submit their histological slides for independent assessment If the issue remains clouded after this analysis then the case for a prospective randomized trial would be much stronger.

J. P. Neoptolemos*
I. C. Talbot†

**University of Birmingham*
Birmingham
UK

†University of Leicester
Leicester
UK

1. Knox RA, Kingston RD Carcinoma of the ampulla of Vater. *Br J Surg* 1986, 73. 72–3.
2. Talbot IC, Neoptolemos JP, Shaw DE, Carr-Locke D. The histopathology and staging of carcinoma of the ampulla of Vater. *Histopathology* 1988; **12**: 155–65.
3. Neoptolemos JP, Talbot IC, Shaw DE, Carr-Locke DL. Long-term survival after resection of ampullary carcinoma is associated independently with tumor grade and a new staging classification that assesses local invasiveness. *Cancer* 1988, **61**: 1403–7.
4. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater. A clinicopathologic study and pathological staging of 109 cases of carcinoma and 5 cases of adenoma. *Cancer* 1987, **59** 506–15.

Dihydroergotamine and the thromboprophylactic effect of dextran 70 in emergency hip surgery

Sir

In the April issue (*Br J Surg* 1988; 75: 364–5) an interesting investigation is reported by Rørbaek-Madsen *et al* analysing whether or not the addition of dihydroergotamine potentiates the thromboprophylactic effect of dextran in patients undergoing surgery for hip fracture. As the study was stimulated by our findings previously published in *The British Journal of Surgery*[1] we would like to make two comments.

Firstly, our findings were based on subgroup analysis in a rather small patient sample and the additive effect of dihydroergotamine and dextran was seen only in hip fracture patients. Moreover, we used ^{125}I-labelled fibrinogen test for the diagnosis of thrombosis. This test is maybe suboptimal in hip fracture patients. It was obvious that our observation had to be reproduced before a firm recommendation could be made on the combined use of dihydroergotamine and dextran for thromboprophylaxis in hip fracture patients. We therefore immediately started a prospective study using phlebographic diagnosis for thrombosis. This study was published in 1985 (Fredin *et al.*[2]) and just as Rørbaek-Madsen *et al* we could not verify our previous findings

Secondly, although our findings are in agreement, we are somewhat concerned about the diagnostic as well as the prophylactic method used by Rørbaek-Madsen *et al.* The motivation to use Tc-plasmin scintigraphy was that 'the same methodological set-up' was to be used as in our previous study. We used the fibrinogen uptake test and as far as we know plasmin scintigraphy has not been adequately evaluated as a prospective diagnostic tool in screening high risk patient populations, such as patients undergoing emergency hip surgery. Further, in our study dihydroergotamine was started immediately after admission if indicated by randomization and not at premedication as in the study by Rørbaek-Madsen *et al.*

D. Bergqvist
H. Fredin
B. Lindblad

General Hospital
Malmo
Sweden

1. Bergqvist D, Lindblad B, Ljungström K-G, Persson N, Hallböök T. Does dihydroergotamine potentiate the thromboprophylactic effect of dextran? A controlled prospective study in general and hip surgery. *Br J Surg* 1984; **71**. 516–21
2. Fredin H, Lindblad B, Jaroszewski H, Bergqvist D. Prevention of the thrombosis after hip fracture surgery. Comparison of dextran 70 with and without dihydroergotamine. *Acta Chir Scand* 1985; **151**: 681–4.

Book reviews

Surgery of the Stomach, Duodenum and Small Intestine

H. Williams Scott. 220 × 282 mm. Pp. 974 Illustrated. 1987. London· Blackwell Scientific Publications £125.00

This book is a massive description of diseases of the stomach, duodenum and small intestine which have surgical implications. Apart from the 2 editors, there are over 70 other contributors who are, without exception, recognized experts in their own fields The book is predominantly American, but there are contributions from Professor Ivan Johnston and John Goligher in Britain and Fritz Holle from West Germany The first section of the book is historical and Dr Herrington's scholarly description of the growth of surgery of the stomach and duodenum is, to my mind, the best ever written. However, there is no question of getting over the history in this section and leaving it out of the others! Most of the subsequent chapters pay more than lip-service to the historical perspective, and their descriptions of the present situation benefit greatly from this approach.

The stated objective of the editors 'is to present a concise yet complete coverage of the surgical problems of the stomach, duodenum and small intestine in more depth than is usually presented in textbooks of surgery or gastroenterology'. For any one reviewer, it would be impertinent to state how completely they have fulfilled their objective because no single reviewer would be competent to critize more than a very few of the 52 chapters. All I can record is that in the chapters on subjects that I do know something about—gastric secretion (Thirlby), gastric empyting and motility (Ritchie and Perez), stress ulcers (Silen), recurrent ulcer (George L. Jordan) and postgastric operations sequelae (the editors)—the descriptions are clear, the coverage complete, and the advice helpful.

The production of the book in terms of format, paper and illustrations is impeccable and I suspect that the editors have put a tremendous amount of work into unifying the approach and style of their contributors. Of course, the book is expensive, but no one who considers himself to be an expert in diseases of this area, or who wishes to make himself into one, can afford not to have easy access to it.

M. Hobsley

Professor of Surgery
University College and Middlesex School of Medicine
London W1
UK

Plastic Surgery in Paediatrics

I. F. K. Muir. 192 × 252 mm. P. 188 Illustrated. 1987. London. Edward Arnold. £49.50.

Ian Muir, the author of this slim volume together with five colleagues from The Royal Aberdeen Children's Hospital, has a professional lifetime's experience of reconstructive surgery in children. The general layout is excellent with bold, useful headings, clear line diagrams and many black and white photographs. In addition, a selection of concise case histories illustrate the fate of many conditions with and without treatment. The essential difference between treating adults and children, i.e. the influence of growth and development, is emphasized throughout. A useful bibliography is provided after each chapter The introduction provides a simple classification of congenital deformity and a broad outline of genetic and embryological faults. Thereafter, eight chapters cover the range of congenital defects which present to plastic surgeons in a systematic manner. One-third of the book is given to the problems of treating cleft lip and palate, reflecting the author's particular interest, but other major contributions deal with the hand and genito-urinary abnormalities. Particular clarity is given to a very confused subject in the chapter dealing with hamartomata. Finally, there is a short discussion of wound healing and basic plastic surgical techniques which might have been better placed earlier in the book Criticisms centre on the difficulties of condensing a large subject into a small book. It can be no more than an introduction for a trainee plastic surgeon but there is too much detail of operative techniques for others Craniofacial deformities are poorly covered with no mention of the importance of early referral to a specialist centre

B. Jones

Consultant Plastic Surgeon
Great Ormond Street
London WC1
UK

Adult and Pediatric Urology (2 Volumes)

J Y. Gillenwater. 220 × 285 mm. Pp. 2088 Illustrated. 1987. Chicago Year Book Medical Publishers. £168 00

This is the latest in the line of mega-textbooks in urology The standard until 10 years ago was Campbell's *Urology* currently in three volumes which has recently appeared in its latest edition Against this American gold standard, John Blandy produced his two volume textbook in the 70s and the latest British contribution is by Whitfield and Hendry to serve the 80s. The Blandy book is sadly out of date now with no sign of a future edition, and so essentially this textbook competes with the British 'Whitfield and Hendry', also in two volumes, and the three volumes of Campbell's *Urology*.

In many ways the layout of the book is standard Indeed, it would be nice to find a post-graduate textbook that did not start off with a chapter on anatomy which, I suspect, nobody ever reads It then works through every aspect of urology, in much the same way as one would expect, subject by subject, with very few non-Americans making any contribution

There are, however, some differences from the standard pattern. the first is the conception of the book—that it should be updated annually by the *Year Book in Urology* to ensure constant updating and revision. Secondly, odd general chapters creep in on para-urological subjects which are, in general, of a higher standard than the rest. In this category, there are chapters on the biology of wound repair and infection, and on malignant disease in general Finally, there are chapters with a more functional rather than anatomical approach, e.g on voiding function and dysfunction and on the principles of paediatric urinary reconstruction, which again are of a higher than average standard.

Any reviewer must automatically go to his pet subject—usually with the intention of tearing holes in it—so I was interested to read the chapter on 'the principles of paediatric urinary reconstruction' by Howard Snyder. This was an outstanding chapter (although the word 'paediatric' could have been dropped from the title) and quite the best in the book as far as I was concerned Indeed, the paediatric urology section as a whole is good, although I thought the chapter on myelomeningocele and the neuropathic bladder was rather weak, but this is another pet subject of mine. The problem with Campbell's *Urology* (in my view) which must be the main competitor for this pair of books is that it tends to be encyclopaediac to the point of losing emphasis on the important issues in the subjects covered by each chapter. Furthermore, it is always the same old names writing on the same old subjects, and there is the constant feeling that you have read it all before, somewhere, but you can't remember where.

The Editors of the present book seem to have tried to inject some new blood into the major subjects, which are fairly well treated, although the more peripheral subjects seem to be less well authored and these, by their sheer number, tend to lower the quality of the book overall. The chapter on bladder cancer was very good, the chapters on voiding function were good, and the benign and malignant prostate and the problems of stone disease were also treated well

I always find American books, chapters and papers parochial in the extreme with little or no reference to the literature outside their own journals and little use of non-American authors This is a shame, not only because it makes somewhat stultifying reading but also because the main impetus in urological research and clinical practice in recent years has shifted away from America, very much to Europe and to Germany in particular. It would have been nice therefore to see this reflected in the selection of authors. On the other hand, one has to acknowledge that America has the major market for books such as this, and this factor alone will have a significant influence on any editor or author

My other main criticism of American books in general, and this one is no exception, is the tendency for authors to reproduce illustrations from other people's work rather than to have illustrations redrawn, and this makes the standard of illustration overall rather erratic, again, it tends to make you feel that you are reading something that you have read before somewhere else

On balance, I am not impressed with this book, but it has displaced Campbell's *Urology* from my book shelf. I do not think there is much to choose between it and 'Whitfield and Hendry', except that I am sure paediatric urologists will prefer this volume—but then I doubt whether they would choose a book like this anyway.

A. R. Mundy

Consultant Urologist
Institute of Urology
London WC2H 8JE
UK

Notices and announcements

28 August–1 September 1988
Fifth World Conference on Lung Cancer
Interlaken, Switzerland
Information. Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basle, Switzerland

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information. Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

4–8 September 1988
11th Annual Meeting of the European Neuroscience Association
Zurich, Switzerland
Information 11th Annual Meeting of the European Neuroscience Association, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

8–10 September 1988
Annual Meeting of the Association of Surgeons in Training
Belfast, UK
Information. Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

10–18 September 1988
Fourth Annual Fall Ultrasound Symposia
London, UK
Information· Annual Fall Ultrasound Meeting, Medical Seminars International Inc., 21915 Rosco Boulevard, Suite 222, Canoga Park, California 91304, USA

12–14 September 1988
International Hepatobiliary Pancreatic Association
Nice, France
Information Dr Jean Mouiel. Department of Surgery, Hôpital Saint Roch–BP319, 06006 Nice Cedex, France

14–16 September 1988
Royal College of Surgeons of England Annual Meeting of Fellows and Members
Cambridge, UK
Information. Secretary, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

14–17 September 1988
9th European Immunology Meeting
Rome, Italy
Information MGA Via P Cossa, 41 00193 Rome, Italy

18–23 September 1988
The Second Oxbridge Organ Transplantation Course
Cambridge, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1988
Oxford Postgraduate Seminar on Early Intervention in Major Trauma
Oxford, UK
Information· Dr P. Nash, Casualty Surgeons Association, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–30 September 1988
Royal Microscopical Society Ultrastructural Anatomy Course
Belfast, UK
Information. The Administrator, Royal Microscopal Society, 37/38 St Clements, Oxford OX4 1AJ, UK

5–8 October 1988
4th Congress of the European Society of Surgical Oncology (ESSO 88)
Paris, France
Information ESSO - 88, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France

5–8 October 1988
4. Jahrestagung Der Deutschen Gesellschaft Für Lasermedizin
Vienna, Austria
Information Doz Dr A Tuchmann, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Vienna, Austria

20 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

24–27 October 1988
American College of Surgeons Meeting: 74th Clinical Congress
Chicago, USA
Information Fred C. Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

30 October–1 November 1988
13th Congress of the European Society for Medical Oncology (ESMO)
Lugano, Switzerland
Information Dr F Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

4–7 November 1988
Integrated Management of Head and Neck Cancer
Grantham, UK
Information. Mr P. J Bradley, Consultant ENT Surgeon/Head and Neck Oncologist, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK

17–19 November 1988
Eighth Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information. Mrs Marty May, Secretary to LTC Warren, F. Bowland MD, Chief, Trauma Service, Department of Surgery, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

25–26 November 1988
European Symposium on Ultrasonic Radiation Safety
Copenhagen, Denmark
Information Mrs A. G. Thorn, Ultrasound Laboratory, Glostrup Hospital, DK 2600 Glostrup, Denmark

25–27 November 1988
22nd Annual Combined Surgical Meeting
Singapore
Information. The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

8th December 1988
British Association of Surgical Oncology Forum: 'Head and Neck Cancer for the General Surgeon'
London, UK
Information: British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–18 December 1988
Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons
Las Vegas, USA
Information· Dr M. R Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988
Association of Surgeons of India Golden Jubilee Annual Conference
New Delhi, India
Information: Dr N. C. Madan, Organizing Secretary 'ASICON-88', Room No. 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

17–19 February 1989
The Fifth Biennial Conference of the Indian Association of Chemotherapists
Bombay, India
Information. Dr Nagraj G. Huilgol MD, Organizing Secretary, Nanavati Hospital and Medical Research Centre, S.V Road, Vile Parle (West), Bombay 400 056, India

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information· Congress Secretariat, 7th Congress Asian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

Contents

The
American
Journal
of
Surgery

JULY 1988/VOLUME 156/NUMBER 1

EDITORIAL OPINION

1 **Surgery, Recall Antigens, Immunity, and Bacillus Calmette-Guerin Vaccination.**
Sol Roy Rosenthal

DIAGNOSTIC IMAGING TECHNIQUES

4 **Diagnostic Imaging Techniques in Mediastinal Malignancies.**
Poonam Batra, Kathleen Brown, and Richard Steckel

SCIENTIFIC PAPERS

11 **Early Diagnosis of Iliofemoral Venous Thrombosis by Doppler Examination.**
Stephen L. Hill, Donna Martin, Eugene R. McDannald, Jr., and Antonio T. Donato

16 **Colon Trauma: Further Support for Primary Repair.**
Salem M. George, Jr., Timothy C. Fabian, and Eugene C. Mangiante

21 **Gastric Juice Factors After Roux-Y Reconstruction Compared With Billroth II Partial Gastrectomy.**
David L. Morris, Valerie Poxon, Denise Youngs, and Michael Keighley

26 **Triglyceride and Cholesterol Content in Bile, Blood, and Gallbladder Wall.**
Italo Braghetto, Cristina Antezana, Carmen Hurtado, and Attila Csendes

29 **Increased Platelet Count as a Screening Test for Distal Splenorenal Shunt Patency.**
Nobuhiro Koyanagi, Yasunori Iso, Hideya Higashi, Seigo Kitano, and Keizo Sugimachi
33 **Editorial Comment**
William J. Millikan, Jr.

34 **Cervical Esophageal Web Associated With Zenker's Diverticulum.**
Donald E. Low and Lucius D. Hill

38 **The Practicing Doctor's Perspective on the Surgical Curriculum.**
Richard K. Reznick, Michael L. Brewer, Robert M. Wesley, David L. Spencer, and J. Roland Folse
43 **Editorial Comment**
J. Roland Folse

44 **Squamous Cell Carcinoma of the Thyroid Gland.**
W. John Simpson and Jack Carruthers

47 **Behavior of Plasma Phospholipase A_2 Activity in Experimental Acute Pancreatitis According to Diet.**
O. Juhani Rämö, Tom Schröder, Anu Mäkelä, and Pekka Jalovaara

51 **Intraabdominal Operations in Patients With Leukemia.**
Edward A. Vaughn, Charles R. Key, and William A. Sterling, Jr.

54 **Thoracic Outlet Syndrome.**
Frank W. Sellke and Thomas R. Kelly

58 **Preoperative Irradiation and 5-Fluorouracil Suppository for Carcinoma of the Rectum.**
Toshio Takahashi, Hirokazu Mizusawa, Toshiro Kato, and Toshiharu Yamaguchi

63 **Predicting the Need for Prolonged Enteral Supplementation in the Patient with Head and Neck Cancer.**
Robert L. Gardine, William A. Kokal, J. David Beatty, Daniel U. Riihimaki, Lawrence D. Wagman, and Jose J. Terz

HOW I DO IT

66 **Splayed Handle Surgical Scissors.**
Michael A. Towler, Michael R. Abidin, Robert W. Cantrell, John G. Thacker, and Richard F. Edlich

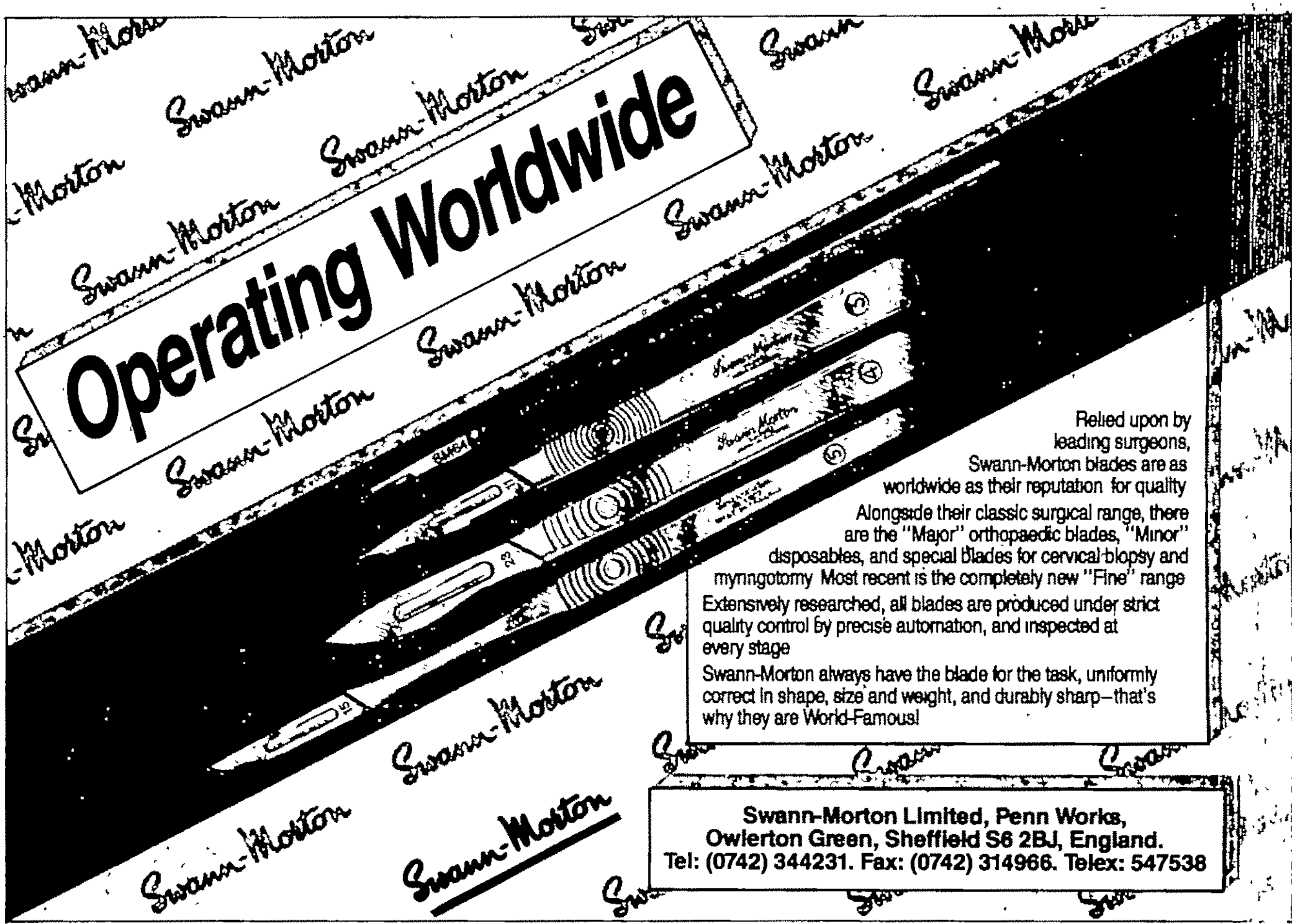
SURGICAL PHARMACOLOGY

68 **Use of Serum Drug Concentrations in Surgical Patients.**
John E. Connors, Joseph T. DiPiro, and John F. Sisley

77 **Book Reviews**

78 ***The British Journal of Surgery* Table of Contents (vol. 75, no. 7, July 1988)**

A9 **Information for Authors**



Relied upon by
leading surgeons,
Swann-Morton blades are as
worldwide as their reputation for quality

Alongside their classic surgical range, there
are the "Major" orthopaedic blades, "Minor"
disposables, and special blades for cervical biopsy and
myringotomy Most recent is the completely new "Fine" range

Extensively researched, all blades are produced under strict
quality control by precise automation, and inspected at
every stage

Swann-Morton always have the blade for the task, uniformly
correct in shape, size and weight, and durably sharp—that's
why they are World-Famous!

Swann-Morton Limited, Penn Works,
Owlerton Green, Sheffield S6 2BJ, England.
Tel: (0742) 344231. Fax: (0742) 314966. Telex: 547538

The St. Mark's Hospital Lecture Course

10th October - 14th October 1988

S! MARK'S

COLOPROCTOLOGY AND THE PELVIC FLOOR

A surgically orientated programme with lectures, case presentations, guest speakers and closed circuit T.V. surgical demonstrations.

Course Fee £150

Further details from:
The Dean's Assistant
St. Mark's Hospital
City Rd. London EC1V 2PS

Tel. 01-253 1050 x4087

Approved for Study Leave HM (67) 27

NEW FROM BUTTERWORTHS . . .

Atlas of Duplex Ultrasonography

Sergio X Salles-Cunha PhD **George Andros** MD

- ★ **the definitive reference for vascular surgeons, medical physicists and radiologists**
- ★ **high quality duplex scans correlated with explanatory diagrams, arteriograms and surgical specimens**
- ★ **offers practical guidance for optimum results**
- ★ **combines the experience and expertise of leading clinical and research laboratories**

Concise Contents:

Arterial Studies · Extracranial Cerebrovasculature in the Neck · Lower extremities · Abdomen · Upper extremities · **Venous Scanning** · Lower extremities · Upper extremities · **Special Studies** · Appendix 1 · Appendix 2

May 1988 192 pp 203 x 235 mm
Hardcover Illustrated 0 941022 08 0
£60.00
A Butterworths/Appleton Davies publication

Please order this title from your usual bookseller or in case of difficulty use the coupon below.

Butterworths

ORDER FORM

To: Felicity Davie, Butterworth Scientific Ltd, PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK

Cash or credit card details with order are essential except for account customers. Overseas orders not accompanied by a remittance will be charged postage and packing.

Please send me ________ copy(s) of **Atlas of Duplex Ultrasonography**
0 941022 08 0 £60.00
Please select preferred method of payment:
☐ I enclose remittance for £ ________
☐ Please debit my credit card as follows
☐ Access ☐ Barclaycard and other Visa cards ☐ American Express
Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Expiry Date ________ Signature ________
☐ Please include me on your mailing list

Name ________
Position ________
Address ________
____
________ Postcode ________

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. In the UK please allow 21 days for delivery.
Registered office: 88 Kingsway, London WC2B 6AB Registered in England No 125354

Butterworths
meeting professional needs

30.4.88

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Editorial Committee

Chairman
C. W. Jamieson, *London*

Vice-Chairmen
J L. Dawson, *London*
H. B. Devlin, *Stockton-on-Tees*

Editors
R. C. G. Russell, *London*
D. C. Carter, *Glasgow*

Associate Editor
A. E. Young, *London*
Statistical Consultant
G. D Murray, *Glasgow*
Editorial Secretary
Lynne Ponjee

T. Bates, *Ashford*
K. G. Burnand, *London*
(*Surgical Research Society*)
J. D. Hardcastle, *Nottingham*
A. G. Johnson, *Sheffield*
M. R. B. Keighley, *Birmingham*
J. A. P. Marston, *London*
A. N. Nicolaides, *London*
(*Royal Colleges of Surgeons*)
I. Taylor, *Southampton*
(*Association of Surgeons*)
N. S. Williams, *London*
R. C. N. Williamson, *London*

Editorial Board

A. P. R. Aluwihare, *Sri Lanka*
E. Q. Archampong, *Ghana*
J. H. Baron, *London*
J. Bergan, *USA*
K. Bielecki, *Poland*
H. Bismuth, *France*
P. C. Bornman, *South Africa*
D. Bouchier-Hayes, *Dublin*
W. H. Brummelkamp, *The Netherlands*
R. Carpenter, *Jamaica*
A. Cuschieri, *Dundee*
R. Dionigi, *Italy*
B. Eklof, *Kuwait*
E. A. Elebute, *Nigeria*
J. R. Farndon, *Newcastle upon Tyne*
J. M. Fitzpatrick, *Dublin*
Sir Patrick Forrest, *Edinburgh*
W. D. George, *Glasgow*
G. R. Giles, *Leeds*
I E. Gillespie, *Manchester*
B. C. Golematis, *Greece*
J. F. Grenier, *France*
A. Habr-Gama, *Brazil*
D. Hanania, *Jordan*
F. Harder, *Switzerland*
M. A. Hassan, *Sudan*
R. J. Heald, *Basingstoke*
G. L. Hill, *New Zealand*
T. Hirayama, *Japan*
M. Horrocks, *Bristol*
E. R. Howard, *London*
L. Hulten, *Sweden*
M. H. Irving, *Manchester*
G. G. Jamieson, *Australia*
J. Jeekel, *The Netherlands*
H -E. Jensen, *Denmark*
Jin-Pok Kim, *Korea*
K. A. Kelly, *USA*
J. A. Mannick, *USA*
T. G. Parks, *Belfast*
A. Pausawasdi, *Thailand*
C. Pera, *Spain*
H. C. Polk, *USA*
A. T. Raftery, *Sheffield*
N. Rangabashyam, *India*
J. H. C. Ranson, *USA*
C V. Ruckley, *Edinburgh*
S. Shionoya, *Japan*
J. C. Smith, *Oxford*
K. Somasundaram, *Malaysia*
T. E. Starzl, *USA*
H. Stone, *USA*
D. E. Strandness Jr, *USA*
G. Teasdale, *Glasgow*
M. Trede, *West Germany*
D. E. F. Tweedle, *Manchester*
A. Watson, *Lancaster*
R. W. Webb, *USA*
D. J. T. Webster, *Cardiff*
F. R. Wilkes, *Armed Forces*
D. Wilmore, *USA*
J. Wong, *Hong Kong*
R. F. M. Wood, *London*

The British Journal of Surgery is published monthly by Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 300966 Telegrams and Telex 859556 SCITEC G Facsimile 0483 301563 Registered office Butterworth Scientific Limited, 88 Kingsway, London WC2 6AB, UK

All queries regarding submitted papers not yet accepted for publication should be addressed to Lynne Ponjee, Editorial Secretary, Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 301439 Telegrams and Telex 859556 SCITEC G Facsimile 0483 301563

Managing Editor Sarah Graham-Campbell
Sub-Editor June Greig-Smith
Production Julia Sentance
Advertisement Sales Representative Mark Butler

UK and Overseas subscription orders should be sent to Westbury Subscription Services, PO Box 101, Sevenoaks, Kent TN15 8PL, UK Telephone 0732 885833 Telex 95678 Facsimile 0732 884079 Cable: Westbury, Sevenoaks, Kent **North American orders** should be sent to Journals Fulfilment Department, Butterworths, 80 Montvale Avenue, Stoneham, MA 02180, USA Telex 880052 Telephone (617) 438 8464

The annual subscription to **The British Journal of Surgery** (12 issues) for UK readers is £65 00, single copies £6 00 and personal subscription £49 00 Overseas rates are annual subscription £78 00, single copies £8 00 and personal subscription £49 00 These prices include delivery by sea mail, air mail rates are available on request For North America rates are annual subscription £78 00, single copies £8 00, personal subscription £49 00 Copies of this journal sent to subscribers in Australasia, Bangladesh, Canada, India, Pakistan, Sri Lanka and USA are air-speeded for quicker delivery at no extra cost

Back issues prior to the current volume are available from Wm Dawson & Sons Ltd, Cannon House, Folkestone, Kent, England CT19 5EE Telephone 0303 57421

US mailing agents Mercury Airfreight International Ltd Inc Second class postage paid at Rahway, New Jersey, USA Postmaster: send address corrections to *The British Journal of Surgery*, c/o Mercury Airfreight International Ltd Inc, 10B Englehard Avenue, Avenel, New Jersey 07001, USA

A microfilm version of **The British Journal of Surgery** is available Please contact University Micro Films Inc, 300 N Zeed Road, Ann Arbor, Michigan, Michigan 48106, USA

Copyright: Readers who require copies (minimum quantity 100) of papers published in this journal may either purchase reprints or obtain permission to copy from the publisher For readers in the USA, permission to copy is given on the condition that the copier pays the stated per copy fee through the Copyright Clearance Center Inc, 27 Congress Street, Salem, Massachusetts 01970, USA (617) 744 3350 for copying beyond that permitted by Sections 107 and 108 of the US Copyright Law Fees appear in the code given at the foot of the first page of each paper This journal is listed in 'Current Contents'

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the Publisher

ISSN 0007-1323

Filmset by Mid-County Press, London SW15 Printed by The Friary Press Ltd, Dorchester and London

Instructions to authors

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another Journal, has not been accepted for publication elsewhere and has not already been published. Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies (one of which must be the top copy) of original articles and other editorial matter to: *The Editor, c/o Lynne Ponjee, The Editorial Secretary, Butterworth Scientific Ltd., PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK. Telephone number: 0483 301439.*

A covering letter must be signed by all authors and must state: if an abstract of the work has been published; and whether the manuscript and/or illustrations are to be returned. Books for review should also be sent to this address.

The first named author is responsible for ensuring that any other authors have seen and approved the manuscript and are fully conversant with its contents.

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. When quoting specific materials, equipment and proprietary drugs, authors must acknowledge the manufacturer but generic names should normally be used.

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65 or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from the Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR (enclose 50p).

Typescripts

Papers should be typewritten on A4 paper (210 × 297 mm) with double spacing and 4 cm margins. Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations.

Title page

The title page should give: (1) title of the article; (2) names and initials of each author with their highest academic qualifications; (3) the department and institution to which the work should be attributed; (4) name and address of author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; (6) keywords.

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytic methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Each table with an appropriately brief title should be typed on a separate page. Illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. Three copies of all illustrations should be submitted. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full, permission having been granted by the author and by the publisher.

Text

The text should usually (but not exclusively) be organized into: introduction, patients/materials and methods, results, discussion.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text but must be clearly defined.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached.

Numbers and units

The decimal point, not a comma, is used, ie 5·7. A space and not a comma follows thousands and multiples thereof, ie, 10 000. SI units (International system of units) are to be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

Statistics

Emphasis will be placed on the correct use of statistics and the statistical methods employed should be described in the methods section of the manuscript.

References

In the text, references should be numbered consecutively by superscript: 1,2 or 1–3. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication, volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s), chapter title, edition, book title, place of publication, publisher, year of publication, page numbers, for example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In :Meyers M, Ghahremani G, eds *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag 1981: 123–63.

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Volume 75 Number 9 September 1988

LEADING ARTICLES

Surgical treatment for thyrotoxicosis **833**
T. S. Reeve

Prevention of postoperative deep vein thrombosis **835**
N. L. Browse

REVIEW

Cyclical mastopathy: a critical review of therapy **837**
P. J. Goodwin, M. Neelam and F. Boyd

Dosage and duration of tamoxifen treatment for mastalgia: a controlled trial **845**
I. S. Fentiman, M. Caleffi, H. Hamed and M. A. Chaudary

Use of fine needle aspiration cytology with immediate reporting in the diagnosis of breast disease **847**
S. Nicholson, J. R. C. Sainsbury, V. Wadehra, G. K. Needham and J. R. Farndon

Role of Doppler ultrasound flowmetry in the diagnosis of breast lumps **851**
A. Srivastava, D. J. T. Webster, J. P. Woodcock, S. Shrotria, R. E. Mansel and L. E. Hughes

Effect of intraperitoneal saline irrigation at different temperatures on adhesion formation **854**
A. M. Kappas, M. Fatouros, K. Papadimitriou, V. Katsouyannopoulos and D. Cassioumis

Ten-year computerized audit of infection after abdominal surgery **857**
Z. H. Krukowski and N. A. Matheson

Pyogenic liver abscess: an improvement in prognosis **862**
O. Farges, T. Leese and H. Bismuth

Pulsatile varicose veins (short note) **865**
R. L. Blackett and G. E. Heard

Anterior lesser curve seromyotomy and posterior truncal vagotomy and posterior truncal vagotomy for chronic duodenal ulcer: the results at five years **866**
A. K. Siriwardena and A. A. Gunn

Highly selective vagotomy: a 14-year experience **869**
D. J. Byrne, B. M. Brock, A. G. Morgan and W. A. F. McAdam

Hyperparathyroidism after neck irradiation **873**
T. J. Christmas, C. R. Chapple, J. G. Noble, E. J. G. Milroy and A. G. A. Cowie

Resting energy expenditure in the critically ill: estimations *versus* measurement **875**
D. C. Hunter, T. Jaksic, D. Lewis, P. N. Benotti, G. L. Blackburn and B. R. Bistrian

Retroperitoneal extravasation from perforated duodenal ulcer (case report) **878**
W. H. Weston-Davies, M. Pertkiewicz and B. Szczygiel

Grip strength: a measure of the proportion of protein loss in surgical patients **880**
J. A. Windsor and G. L. Hill

Neutrophil degranulation and increased pulmonary capillary permeability following oesophagectomy: a model of early lung injury in man **883**
G. M. Rocker, M. S. Wiseman, D. Pearson and D. J. Shale

Left gastric venous caval shunt with externally reinforced polytetrafluoroethylene graft (surgical workshop) **886**
J. Kambayashi, Y. Tsuji, M. Danno, T. Ohshiro and T. Mori

Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis **888**
D. Bergqvist, T. Mätzsch, U. S. Burmark, J. Frisell, O. Guilbaud, T. Hallböök, A. Horn, A. Lindhagen, H. Ljungnér, K.-G. Ljungström, H. Onarheim, B. Risberg, S. Törngren and P. Örtenwall

Choledochal cyst: a 14-year surgical experience with 36 patients 892
K. C. Tan and E. R. Howard

Endoscopic removal of retained stones after biliary surgery 896
M. E. Lambert, D. F. Martin and D. E. F. Tweedle

Cholelithiasis: a serious complication after total gastrectomy 899
P. Hauters, A. de Neve de Roden, A. Pourbaix, F. Aupaix, P. Coumans and G. Therasse

FOR DEBATE

Definitive radiation therapy for selected cancers of the rectum 901
B. Sischy, E. J. Hinson and D. Wilkinson

An aetiology for fistula *in ano* 904
I. K. Pople and D. N. L. Ralphs

Proliferation patterns and aneuploidy in adenomatous polyps of the colon 906
J. Matthews, S. Sousha, R. A. Parkins, M. Glynn and T. Cooke

Villous tumours of the large bowel 910
S. G. Pollard, R. Macfarlane and W. G. Everett

New technique of anastomosis after resection of left colon and rectum 913
V. I. Korepanov, R. Sh. Chuntua and S. P. Sugrobov

Diagnosis and management of graft–enteric fistulae 915
H. W. Tilanus, O. T. Terpstra, P. de Smit, H. van Urk and H. F. Veen

Rectus nerve entrapment causing abdominal pain (short note) 917
P. N. Hall and A. P. B. Lee

Wound infection after breast biopsy (short note) 918
J. M. Dixon, U. Chetty and A. P. M. Forrest

Misdiagnosis of breast cancer in an out-patient breast clinic (short note) 920
E. Siim, J. Kjaergaard, F. Rank, H. Baden and B. Lundbæk

Ultrasound scanning by the urologist in outpatient clinics (short note) 921
S. G. Vesey, P. J. O'Boyle and G. N. Lumb

Continuous wound perfusion with bupivacaine for postoperative wound pain (short note) 923
P. Gibbs, A. Purushotham, C. Auld and R. J. Cuschieri

Oral pancreatic enzymes accelerate closure of external pancreatic fistulae (short note) 924
A. M. García-Pugés, S. Navarro, L. Fernández-Cruz, E. Ros, L. Hinojosa and C. Pera

BRITISH SOCIETY OF ENDOCRINE SURGEONS 926

CORRESPONDENCE 931

BOOK REVIEWS 933

NOTICES AND ANNOUNCEMENTS 936

Cover picture

Lord Moynihan Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA)

Br. J. Surg. 1988, Vol. 75, September, 833–834

Surgical treatment for thyrotoxicosis

Thyrotoxicosis has been known to man for centuries with descriptions dating back to the Mayan period in Peru. It is a disease that presents in many guises, ranging from apathy to mania and the diagnosis can, on occasions, be a test for even the most competent clinician. It is usually associated with the presence of a significant goitre but even that clue may not be present in Graves' disease. Thyrotoxicosis generally presents in one of three forms: diffuse goitre with auto-immune features; toxic single nodular goitre; or toxic multinodular goitre.

Graves' disease is associated with an immunoregulatory disturbance and the presence of a thyroid stimulating immunoglobulin. In its most florid form Graves' disease manifests the perplexing symptoms of thyrotoxicosis, a diffuse goitre, thyroid ophthalmopathy and pretibial myxoedema. The disease process ranges from mild to very severe and in former times was frequently life threatening.

Plummer's disease may present as a single toxic (autonomous) nodule or as a multinodular goitre. The disease is more frequent in older patients with a longstanding nodular goitre which proceeds to autonomy with excessive thyroxine secretion.

There are some more unusual causes of thyrotoxicosis of which surgeons should be aware when confronted by a puzzling clinical problem in a patient considered to have hyperthyroxinaemia. Factitious hyperthyroidism owing to excessive ingestion of thyroxine is probably the most common explanation. Thyroiditis of the auto-immune or subacute type also frequently presents with toxic symptoms. Hyperthyroxinaemia may also be produced by functioning metastatic thyroid cancer or trophoblastic tumours which have inappropriate secretion of hormones with thyroid stimulating capacity, e.g.: molar pregnancy, choriocarcinoma, some testicular tumours and struma ovarii.

No patient should be submitted to treatment for thyrotoxicosis unless the diagnosis is substantiated by an appropriate body of diagnostic tests. Careful and accurate diagnosis cannot be over-stressed. There is no prize given for operating on patients with unsuspected uncontrolled hyperthyroidism. Thyroid storm following elective thyroidectomy for hyperthyroidism is not an acceptable complication. Tests to measure thyroxine (T4), tri-iodothyronine (T3), thyroid binding globulin, and thyroid stimulating hormone are readily available and should be used for maximum accuracy in diagnosis. Reliance should never be placed on a single test which cannot be verified. Isotope scanning is a useful means of demonstrating autonomy in the patient with proven toxicity and a single nodule. It is also the most reliable way to differentiate thyroiditis. The thyrotrophin releasing hormone test reliably separates thyrotoxicosis from other causes of hyperthyroxinaemia.

Treatment for the disease was essentially expectant before Kocher introduced thyroidectomy[1]. The operation done in thyrotoxic patients was dangerous, and a full measure of admiration is due to the pioneer surgeons who 'blazed the trail'. Operations on perilously ill patients produced many cures. The surgeons changed techniques and produced instruments that became the basis of modern operating kits. Kocher learned about thyroid and parathyroid excision and the clinical syndromes resulting from them; after he introduced total thyroidectomy he accrued the first Nobel Prize for surgery.

Surgery remained the first choice of treatment until Astwood introduced thiouracil in 1942. Patients could then be controlled and decisions made as to timing of surgery for the 40 per cent whose problems recurred when antithyroid drugs were withdrawn[2]. Radioiodine followed hard on the heels of antithyroid drugs and physicians began to move the disease from the operating room to the consulting room. This was relatively short-sighted since thyroidectomy remains the one therapy that will control the disease within a reasonable time schedule and which results in the lowest possible incidence of hypothyroidism. However, for small uncomplicated toxic goitres, radioiodine has become the treatment of choice[2].

In patients with severe ophthalmopathy, total thyroidectomy removes the target organ and allows the patient to be stabilized. Very large glands in the young are probably better removed totally as they tend to be associated with rapid recurrence of the disease after subtotal thyroidectomy. In childhood, surgery is sound treatment but delaying thyroidectomy until puberty is less traumatic for the child. In pregnancy, radioiodine is contra-indicated as fetal damage may ensue. Blocking agents also cross the placenta and can lead to thyroid enlargement. Surgery in the second trimester offers optimal therapy.

In patients with a multinodular toxic goitre, particularly the elderly, thyrocardiac disease may be present as may a significant degree of tracheal compression. Total thyroidectomy is satisfactory treatment when the nodular disease involves both lobes, provided it can be achieved with minimal complications[3,4]. Both the parathyroid glands and recurrent laryngeal nerves can be protected with minimal morbidity by 'hugging' the capsule during dissection.

Bilateral subtotal thyroidectomy for Graves' disease should result in long term euthyroidism in 60–70 per cent of patients, with low levels of recurrent nerve palsy and hypoparathyroidism when performed by appropriately trained surgeons[5]. It is important, however, that patients are restored to euthyroidism by antithyroid drug administration if thyroidectomy is selected as permanent therapy.

Thyroidectomy blazed the trail for modern surgery. It is now time that surgeons challenged the more conservative use of medical treatment and committed themselves to careful, precise, low morbidity surgery espoused by a previous generation of courageous surgeons who handed the baton down to us.

T. S. Reeve

Royal North Shore Hospital
St. Leonards
New South Wales 2065
Australia

1. Colcock BP. Lest we forget: a story of five surgeons. *Surgery* 1968; **64**: 1162–72
2. Becker DV Choice of therapy for Graves' hyperthyroidism (editorial). *N Engl J Med* 1984; **311**: 464–460.
3. Perzik SL. The place of total thyroidectomy in the management of 909 patients with thyroid disease. *Am J Surg* 1976; **132**: 480–3.
4. Reeve TS. *Surgery for Hyperthyroidism. Adv. Surg.* Chicago: Year Book Publishers Inc., 1987; **21**: 29–48.
5. Klementschitsch P, Shen K, Kaplan E. Re-emergence of thyroidectomy as a treatment for Graves' disease. *Surg Clin North Am* 1979; **59**: 35–44.

Br. J. Surg. 1988, Vol. 75, September, 835–836

Prevention of postoperative deep vein thrombosis

Thirty years ago, Sevitt and Gallagher[1] established that full anticoagulation with an oral anticoagulant significantly reduced the incidence of post-traumatic deep vein thrombosis and pulmonary embolism; but their prophylactic regimen was not widely adopted by general or orthopaedic surgeons because of the logistical problems of haematological control and the unacceptable incidence of bleeding complications.

Between 1971 and 1975, many groups of investigators confirmed that a small dose of heparin given subcutaneously significantly reduced the incidence of deep vein thrombosis and these studies were followed by two large multicentre trials[2,3] which strongly suggested, but did not to my satisfaction conclusively prove, that subcutaneous heparin also reduced the incidence of fatal pulmonary embolism. In the same period many mechanical methods of prophylaxis were studied[4]; the simplest was graduated compression stockings which were found to be almost as effective against deep vein thrombosis as the more complex techniques, but no mechanical method has yet been properly tested against the end points of pulmonary embolism or total mortality.

If there are both pharmacological and mechanical methods which effectively reduce the incidence of deep vein thrombosis why do we not all use them? Overall, the pharmacological methods are more effective than the mechanical methods but the injection of heparin every 12 or 8 h has logistical problems, a small complication rate, and is not always effective particularly after major orthopaedic operations. Consequently, many have been searching for a simpler and hopefully still more effective pharmacological alternative. Low molecular weight heparin may be the answer[5]. Two recent papers[6,7] examining over 1200 patients have confirmed that a single daily dose of low molecular weight heparin has the same effect on postoperative deep vein thrombosis as the standard unfractionated heparin regimen with possibly fewer bleeding complications, but this drug still has to be tested for an effect on pulmonary embolism and total mortality.

What should the busy surgeon do? The simplest and most effective way of preventing deep vein thrombosis after general surgical operations on patients over the age of 60 years, in whom bleeding is not a serious surgical risk, is probably subcutaneous low molecular weight heparin daily combined with anti-embolism stockings. High-risk patients in whom bleeding is not a serious hazard may be better protected by full anticoagulation; but in patients where bleeding could be a serious hazard to life or limb, pneumatic compression during the operation plus anti-embolism stockings, though less effective, is safer. Patients under 60 years of age without any special risk factors probably just need stockings and/or intra-operative pneumatic compression.

This scheme can also be applied to orthopaedic patients with the possible addition of dihydroergotamine to the heparin in the hope that it may enhance the effect of the heparin. However, patients undergoing hip replacement surgery will still be at significant risk as they are more resistant to all forms of prophylaxis.

Will these methods abolish deep vein thrombosis and pulmonary embolism? No. No method is 100 per cent effective and in sick patients the deep vein thrombosis may have begun before the prophylaxis is commenced. Thus the administration of a prophylactic regimen should not reduce clinical awareness of the physical signs of deep vein thrombosis or pulmonary embolism, however unreliable they may be, so that secondary prophylaxis can be instituted.

The above opinions are based on my interpretation of the available evidence[8]. The scientist in me still believes that any new regimen should not be adopted before it has been properly tested against pulmonary embolism and total mortality in a large *controlled* clinical trial. However the desire of surgeons to do their best for their patients, their willingness to base their opinions on less than perfect evidence and their subsequent resistance to studies with untreated control patients makes it unlikely that such trials will ever be conducted. The result is an evolving form of treatment which becomes incorporated into medical practice although its value in scientific terms

0007–1323/88/090835–02$3 00

has not been proved—just as many of the other indications for the exhibition of anticoagulants are unsubstantiated. I hope that someone someday will not prove that we have got it wrong.

N. L. Browse

St. Thomas' Hospital
London SE1 7EH
UK

1. Sevitt S, Gallagher NG. Prevention of venous thrombosus and pulmonary embolism in injured patients. *Lancet* 1959, **ii**: 981–9.
2. An international multicentre trial. Prevention of fatal pulmonary embolism by low doses of heparin *Lancet* 1975; **ii**: 45–51.
3. Gruber VF, Saldeen T, Brokop T *et al.* Incidence of fatal post-operative pulmonary embolism with Dextron 70 and low dose heparin: *Br Med J* 1980; **280**· 69–72.
4. Bergqvist D. *Post-operative Thrombo-Embolism. Frequency, Aetiology and Prophylaxis.* New York: Springer-Verlag, 1983: 67–78.
5 Kakkar VV, Murray WJG. Efficacy and safety of low molecular weight heparin (CV 216) in preventing postoperative venous thrombo-embolism *Br J Surg* 1985; **72** 786–91.
6 Samuma M, Bernard P, Bonnardot JP, Combe-Tamzal S, Lanson Y, Tuisot E. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *Br J Surg* 1988; **75**: 128–31.
7. Lassen MR, Borris LC, Christiansen H *et al.* Heparin/dihydrogotamine for venous thrombosis prophylaxis· comparison of low-dose heparin and low molecular weight heparin in hip surgery. *Br J Surg* 1988; **75**: 686–9.
8. Browse NL, Burnand KG, Lea Thomas M. *Diseases of the Veins.* London: Edward Arnold, 1988.

Br. J. Surg. 1988, Vol. 75, September, 837–844

Cyclical mastopathy: a critical review of therapy

P. J. Goodwin*, M. Neelam† and N. F. Boyd†

*Henrietta Banting Breast Centre,
Women's College Hospital,
University of Toronto, and
†Ludwig Institute for Cancer
Research (Toronto Branch),
Canada

Correspondence to:
Dr P. J. Goodwin, Department of
Medicine, Women's College
Hospital, 60 Grosvenor Street,
Suite 511, Toronto, Ontario
M5S 1B6, Canada

Because of a recently completed trial which demonstrated that dietary fat reduction improved the symptoms of cyclical mastopathy, we have carried out a critical review of other studies of treatment for this disorder to determine what, if any, mechanisms of action were shared by effective treatments. Therapies were classified as 'definitely effective' if their effectiveness was demonstrated in at least one randomized placebo-controlled study of women with cyclical mastopathy, 'probably effective' if their effectiveness in relieving breast symptoms was demonstrated in at least one study in women with premenstrual syndrome, and 'probably not effective' if they had not been shown to improve breast symptoms in at least two studies in women with premenstrual syndrome. Bromocriptine, danazol, evening primrose oil, tamoxifen and reduction of dietary fat intake were classified as definitely effective and norethisterone and Bellergal as probably effective. Several therapeutic manoeuvres, including reduction of methylxanthine ingestion and the administration of vitamin E or diuretics, have not been adequately evaluated in women with cyclical breast symptoms. A review of the published reports of the physiological effects of therapies that were definitely or probably effective revealed that these agents acted either to alter serum prolactin levels or lipid metabolism, or both. As evidence exists that prolactin influences lipid metabolism it is postulated that cyclical mastopathy may be a disorder of lipid metabolism.

Keywords: Cyclical mastopathy, lipid metabolism, serum prolactin levels

Cyclical mastopathy affects 30–40 per cent of premenopausal women in Western society during their reproductive years; in approximately 8 per cent of these women it is of such severity that it significantly interferes with normal activities[1]. The syndrome comprises breast swelling, tenderness and/or engorgement which typically begin during the luteal phase of the menstrual cycle, increase in intensity as menses approach and then resolve rapidly with the onset of menstrual flow[2] In severe cases symptoms may begin soon after menses during the follicular phase of the cycle, leaving a very brief symptom-free interval around the time of the menstrual period. Cyclical mastopathy is to be differentiated from non-cyclical mastopathy, in which pain does not vary in relation to the menstrual cycle in the manner described above, and from secondary causes of breast pain such as infection, trauma or tumour, in which underlying physical causes for breast pain can be identified. It may occur in association with a symptom complex commonly referred to as the premenstrual syndrome or it may occur in the absence of this syndrome. If both problems are present they may not occur with equal severity and breast symptoms and other components of the premenstrual syndrome may respond differently to treatment[3–12], suggesting that these disorders may be separate entities.

A recently completed randomized study of dietary fat reduction in women with cyclical mastopathy examined the effect of dietary fat reduction on the symptoms of cyclical mastopathy[13,14]. In this trial women with severe cyclical mastopathy of at least 5 years' duration were randomly allocated to a control group that received general dietary advice but were not counselled to change the fat content of their diet (9 women) or to an intervention group who were taught how to reduce the fat content of their diet to 15 per cent of caloric intake while increasing the intake of complex carbohydrates to maintain caloric intake. Both groups were followed for 6 months with food records and measurement of plasma hormone and lipid concentrations. Symptom severity was measured using daily diaries, questionnaires and linear analogue scales. Patients also underwent a physical examination by a physician who was unaware of their dietary status. After 6 months there was a highly significant reduction in the severity of premenstrual breast tenderness ($P = 0{\cdot}0001$) and swelling ($P = 0{\cdot}0002$). These changes in the breast were correlated with changes in plasma cholesterol, which were of borderline statistical significance, but not with changes in serum hormone levels. These results indicate that dietary fat reduction has a striking effect on the symptoms of cyclical mastopathy and suggest that further investigation of the mechanism of action of this intervention is needed.

This observation has prompted us to undertake a critical appraisal of all published trials of therapy of cyclical mastopathy. The purpose of this appraisal was to identify those treatments that are effective and to explore their physiological actions to determine whether evidence for a common mechanism could be found. In the past it has been hypothesized that psychological factors, fluid retention, hormonal imbalances (particularly luteal phase insufficiency or elevated serum prolactin levels) and dietary factors (such as methylxanthine ingestion or Western diets deficient in essential fatty acids) cause cyclical mastopathy[2]. None of these mechanisms is widely accepted and evidence for and against each can be found in the published literature.

Methods: assembly of the literature

A review of the literature was undertaken using Medline to identify reports published in English between 1975 and 1987

---

* *Clinical Trials Scholar of the National Cancer Institue of Canada*

0007-1323/88/090837-08$3 00

Table 1 *Studies in women with cyclical mastopathy*

First author (Ref. no.)	Therapy	Breast abnormality	*n*	Significant improvement in abnormality
Mansel (15)	Bromocriptine	Pain, heaviness, tenderness, discharge	29	Yes
Hinton (16)	Bromocriptine	Pain, heaviness, tenderness	19	Yes
Blichert-Toft (17)	Bromocriptine	Mastalgia	8	Yes
Durning (18)	Bromocriptine	Pain, tenderness, engorgement, etc.	38	Yes
Mansel (19)	Danazol	Tenderness, nodularity, discomfort	28	Yes
Doberl (20)	Danazol	Mastodynia	30	Yes
Hinton (16)	Danazol	Pain, heaviness, tenderness	21	Yes
Mansel (21)	Danazol	Pain, heaviness, tenderness, etc.	6	N/A*
Preece (22)	Evening primrose oil	Pain, tenderness heaviness, etc	41	Yes
Fentiman (23)	Tamoxifen	Pain	57	Yes
Boyd (13, 14)	Dietary fat reduction	Pain, swelling, tenderness, etc.	21	Yes

* Not analysed

Table 2 *Studies in women with the premenstrual syndrome*

First author (Ref. no)	Therapy	Breast abnormality	*n*	Significant improvement in abnormality
Graham (3)	Bromocriptine	Tenderness	10	No
Andersch (24)	Bromocriptine	Swelling	26	No
Elsner (4)	Bromocriptine	Tenderness	24	Yes
Andersen (5)	Bromocriptine	Mastodynia, galactorrhoea	26	Yes
Ylostalo (6)	Bromocriptine	Engorgement	17	Yes
Kullander (25)	Bromocriptine	Mastodynia	10	No
Watts (26)	Danazol	Discomfort	40	N/A*
Gilmore (27)	Danazol	Discomfort	39	N/A*
Puolakka (28)	Evening primrose oil	Tenderness, swelling	24	No
Dennerstein (29)	Progesterone	Tenderness, swelling, discomfort	24	No
Andersch (30)	Progesterone	Swelling	20	No
Haspels (7)	Dydrogesterone	Pain, tenderness	150	No
Ylostalo (6)	Norethisterone	Tenderness, engorgement	19	Yes
Wood (8)	Mefenamic acid	Tenderness	39	No
Gunston (9)	Mefenamic acid	Tenderness	42	No
Werch (10)	Metolazone	Swelling	46	Yes
Carstairs (11)	Tenavoid	Pain	39	No
Robinson (12)	Bellergal	Tenderness	32	Yes

* Not analysed

that dealt with the treatment of cyclical mastopathy or breast pain. Additional Medlines were carried out to identify all reports of therapy of premenstrual syndrome. Additional reports were identified from the references in these reports. Studies were included if they were randomized, placebo-controlled trials which evaluated the effect of the intervention being studied on breast signs and/or symptoms. Studies that examined the effect of therapies on premenstrual syndrome but did not separately identify breast symptoms were excluded. Letters to the editor and abstracts were also excluded.

Reports were grouped into one of three categories according to the clinical entity being studied. These categories were (1) studies involving women with cyclical mastopathy defined according to the criteria outlined above; (2) studies involving women with premenstrual syndrome in whom breast symptoms were reported separately from other premenstrual symptoms, and (3) studies involving women with a variety of breast abnormalities, not defined as cyclical mastopathy. The terms used to describe these entities included benign mastopathy, and 'chronic cystic mastitis'.

Results

Thirty-two reports that satisfied the criteria for inclusion, some of which evaluated more than one treatment, were identified. Of these reports, 9 evaluated the efficacy of various treatments in women whose primary symptom was cyclical mastopathy, 17 evaluated therapy in women with premenstrual syndrome and analysed separately the effect of therapy on breast symptoms, and 6 reports evaluated various therapies in women with other breast abnormalities. These studies are summarized in *Tables 1, 2* and *3*.

Studies in women with cyclical mastopathy

In these studies, which are outlined in *Table 1*, women were recruited if they reported breast symptoms as their primary complaint. Some studies included women with both cyclical and non-cyclical breast complaints but all either analysed the effect of therapy on cyclical breast symptoms separately or provided sufficient data for readers to perform this analysis themselves. The specific complaints evaluated in each study are described in *Table 1*.

As can be seen from *Table 1*, the therapies that were evaluated included bromocriptine (a dopaminergic agonist that inhibits release of prolactin from the pituitary gland), danazol (an 'impeded' androgen), evening primrose oil (an essential fatty acid supplement) and tamoxifen (an anti-oestrogen). The number of women studied and the effect of the therapeutic intervention on breast symptoms are also shown in the Table. For completeness, the study of dietary fat reduction which prompted this critical appraisal is included in this Table. A complete description of this study can be found elsewhere[13,14].

Each of the above therapeutic interventions was shown to be effective in relieving cyclical breast symptoms. Bromocriptine, in a luteal phase dose of 2·5 mg twice daily, was shown to be effective in all four studies which evaluated its effectiveness[15–18].

Table 3 *Studies in women with other breast abnormalities*

First author (Ref no.)	Therapy	Breast abnormality	*n*	Significant improvement in abnormality
Gorins (31)	Danazol	Severe benign mastopathy	45	Yes
Dhont (32)	Danazol	Chronic cystic mastitis	25	Yes
Ernster (33)	Vitamin E	Clinically palpable breast abnormalities	73	No
London (34)	Vitamin E	Mammary dysplasia	135	No
Ernster (35)	Reduction of methylxanthine ingestion	'Breast concerns'	158	Yes
Colin (36)	Lynoestrenol	Radiological and thermal changes consistent with mastodynia	50	Yes

Danazol, in a luteal phase dose of 100–400 mg/day, was shown to be effective in three studies[16,19,20]. In a fourth study of danazol, an improvement in symptoms was seen when danazol was administered but this was not analysed for statistical significance[21]. In one study, which compared the effectiveness of both danazol and bromocriptine with placebo, danazol was found to be significantly more effective than bromocriptine in relieving cyclical breast symptoms[16]. Evening primrose oil (6 capsules per day) was shown to be effective in one study[22] and tamoxifen (20 mg/day) in another[21]. As outlined above, reduction of dietary fat intake from 40 per cent of caloric intake to 20 per cent of caloric intake significantly reduced cyclical breast symptoms when compared with maintenance of usual fat intake[13,14].

Studies in women with premenstrual syndrome

Studies that evaluated the efficacy of various therapies on breast symptoms in women with this syndrome are outlined in *Table 2* with the specific breast symptoms examined. In these studies, the presence of cyclical breast symptoms was not required for entry and some of the breast symptoms that were evaluated may have been either non-cyclical or secondary to some identifiable physical cause. It is likely that many women in these studies had less severe breast symptoms than women in the studies of cyclical mastopathy outlined above, as the latter studies often required that only women with severe symptoms be admitted to the study. Thus, it would be expected that it might be more difficult to detect improvements in breast symptomatology in the premenstrual syndrome studies unless sample sizes were considerably larger, even if the therapy was efficacious.

As can be seen from *Table 2*, the therapies evaluated included bromocriptine (in luteal phase doses of 2·5 mg/day), danazol (in luteal phase doses of 100–400 mg/day), evening primrose oil (6 capsules per day), various progestational agents, the antiprostaglandin mefenamic acid (500 mg three times daily), the diuretic metolazone (5 mg/day) and two combination preparations, Tenavoid which contains a diuretic and a sedative, and Bellergal which contains belladonna alkaloids, ergotamine tartrate and a barbiturate. The number of women studied (if the number of women with breast symptoms was reported, this number was used), and the effect of the therapeutic intervention on breast symptoms are also shown in the Table.

Bromocriptine was shown to be effective in three of six studies[3–6,24,25]. The ability of a study to demonstrate the therapeutic effectiveness of bromocriptine was related to the number of patients studied: three of the four largest studies showed bromocriptine to be an effective therapy whereas the two smaller studies did not. The two studies that evaluated the effect of danazol on breast symptoms in women with premenstrual syndrome both stated that danazol 'significantly' reduced breast symptoms, but it was not clear from the reports whether this conclusion was reached after a statistical analysis[26,27]. These reports are entered as 'not analysed' in the Table. One of the four studies of progestational agents demonstrated a beneficial effect of norethisterone on breast tenderness and engorgement; however, norethisterone was less effective than danazol in relieving these breast symptoms[6]. The other three studies evaluated either progesterone or dydrogesterone and found these agents to be ineffective[7,29,30]. Norethisterone is a progestational agent with androgenic properties and it is possible that the difference in effectiveness is related to this property; this is discussed further below. Bellergal, which contains an ergot preparation that has effects similar to those of bromocriptine, was effective in relieving breast tenderness in one study[12] and metolazone (a diuretic) relieved breast swelling in another[10]. The effect of metolazone on two important components of cyclical mastopathy (breast pain and tenderness) was not examined, therefore this study is not considered further. Evening primrose oil was ineffective in one study[28], mefenamic acid in two[8,9] and Tenavoid in one[11].

Studies in women with other breast abnormalities

Studies which evaluated therapeutic interventions in groups of women who were not recruited on the basis of cyclical mastopathy or premenstrual syndrome are summarized in *Table 3*, in which the breast abnormalities studied are outlined. Some of the women included in these studies may have had cyclical mastopathy; however, others probably had non-cyclical mastopathy and some probably had no significant breast symptoms. Because of the heterogeneous nature of the women studied, it is not advisable to extrapolate the results of these studies to women with the syndrome of cyclical mastopathy. These reports are included because they evaluated treatments commonly believed to be effective in cyclical mastopathy, in order to highlight the fact that the effectiveness of some of these therapies has never been properly evaluated.

As can be seen from *Table 3*, the therapies that were evaluated included danazol, vitamin E, lynoestrenol (a progestational agent) and abstention from methylxanthine ingestion. Danazol improved mastodynia, breast nodularity and thermographic abnormalities in women with severe benign mastopathy[31] and it relieved breast pain and tenderness in women with chronic cystic mastitis[32]. Lynoestrenol improved clinical (physical examination) and thermographic evidence of mastodynia in women with 'radiological and thermal changes characteristic of mastodynia'[36]. Abstention from methylxanthine ingestion improved palpable breast abnormalities and reduced breast cyst fluid caffeine levels in women with 'breast concerns' in one study[35] whereas vitamin E, in doses ranging from 150 to 600 mg/day, had no effect on clinically palpable breast findings or on mammary dysplasia in two studies[33,34].

Classification of therapies according to their effectiveness in cyclical mastopathy

Each of the therapies evaluated was classified according to the strength of the evidence regarding its effectiveness in relieving the symptoms of cyclical mastopathy. Agents were classified as 'definitely effective' if their effectiveness had been demonstrated in at least one study of women with cyclical mastopathy. Agents were classified as 'probably effective' if they had been shown to be effective in relieving breast symptoms in at least one study of women with premenstrual syndrome. Agents were classified as 'probably not effective' if they had been shown to be ineffective in relieving breast symptoms in at least two studies of women with premenstrual syndrome. Unfortunately, none of these agents was evaluated in women recruited on the basis of cyclical mastopathy and future studies may change this classification. However, this is the most appropriate classification based on information currently available. All other agents were considered to have been inadequately evaluated with respect to their efficacy in cyclical mastopathy.

The results of this classification are shown in *Table 4*. Bromocriptine, danazol, evening primrose oil, tamoxifen and reduction of dietary fat intake were classified as 'definitely effective', Bellergal and norethisterone as 'probably effective', and antiprostaglandins and other progestational agents as 'probably not effective'. The effectiveness of diuretics, vitamin E, lynoestrenol, or reduction of methylxanthine ingestion in relieving cyclical breast symptoms has not been adequately evaluated.

Table 4 *Classification of therapies according to their effectiveness in relieving cyclical breast symptoms*

Category	Definition	Therapy
Definitely effective	Effectiveness in relieving cyclical breast symptoms demonstrated in at least one study of women with cyclical mastopathy	Bromocriptine; danazol, evening primrose oil; tamoxifen; dietary fat reduction
Probably effective	Effectiveness in relieving cyclical breast symptoms demonstrated in at least one study of women with cyclical breast symptoms as part of the premenstrual syndrome	Bellergal; norethisterone
Probably not effective	Lack of effectiveness demonstrated in at least two studies of women with cyclical breast symptoms as part of the premenstrual syndrome	Mefenamic acid; progesterone, dydrogesterone
Not adequately evaluated	Effectiveness in relieving cyclical breast symptoms not adequately evaluated	Diuretics; vitamin E, reduction of methylxanthine ingestion; lynoestrenol

Mechanisms of action of effective therapies

The physiological actions of agents classified as definitely effective or probably effective were then examined to determine whether evidence for a common mechanism of action could be found that might provide clues to the pathophysiology of cyclical mastopathy. As the agents that had been identified as effective were either hormonally active or resulted in alterations in dietary fat intake or lipid metabolism, or both, particular emphasis was placed on the effects of the agents on serum hormone and lipid levels. It is recognized that several of the agents have other actions, and that information was not available for all agents regarding their action on hormones and lipids. Further, the physiological changes responsible for clinical efficacy may not have been identified for any of the agents involved. Nevertheless, the information available is summarized in *Table 5*.

As can be seen from *Table 5*, bromocriptine acts primarily as a dopaminergic agonist to decrease prolactin release from the pituitary gland[37]. It appears to have little effect on serum oestrogen[5,6,25,37,38], progesterone[5,6,24,25,37,38], testosterone[6,37], and gonadotrophin levels[6,25,37,38]. Its effect on serum lipids in healthy women is poorly documented. In women with galactorrhoea secondary to hyperprolactinaemia, bromocriptine reduces elevated serum levels of total lipids, triglycerides and cholesterol towards those seen in normal lactating women and it causes similar changes in the lipid content of the mammary secretions obtained from these women[39]. Its effect on specific lipoprotein fractions, in particular high density lipoprotein (HDL) and low density lipoprotein (LDL) is unknown. Bellergal, which contains ergotamine, a compound that acts in a manner similar to bromocriptine, probably has effects on hormone and lipid levels that are similar to those of bromocriptine; however, these are poorly documented.

Danazol, a derivative of 17α-ethinyl-testosterone has effects on several hormones. Reports of its effects on serum hormones are occasionally contradictory. In most studies it has been found to result in reduced serum oestrogen levels[40–42] although this effect has not been seen in all studies[43,44]. It appears to have little effect on serum progesterone[32,43,44]. It reduces sex-hormone binding globulin[41,45,46] and increases testosterone[32,41], effects that probably account for the androgenic effects of the drug. It also alters gonadotrophin secretion, thereby preventing ovulation in premenopausal women. Although the precise nature of this effect on gonadotrophins is controversial, danazol appears to inhibit pulsatile secretion of luteinizing hormone (LH)[40,41,44] and probably follicle-stimulating hormone (FSH) as well[40]. When measured repeatedly, average serum prolactin concentration over a period of 9 days was found to be reduced by danazol in one study[44]. However, when prolactin was measured on one occasion only,

Table 5 *Changes in serum hormones and lipids with agents shown to be effective in cyclical mastopathy*

Agent	Oestrogen	Progesterone	Testosterone	LH/FSH	Prolactin	Lipids
Bromocriptine*	No effect	No effect	No effect	No effect	Decreased	Decreased total lipids, cholesterol and triglycerides in serum and breast secretions of women with galactorrhoea; ? effect in normals
Danazol	Decreased	No effect	Increased	Decreased pulses	Decreased	Decreased HDL (45%), increased LDL
Tamoxifen	Decreased activity	No effect	No effect	No effect†	Decreased	Decreased HDL (chol); decreased LDL (chol), decreased total chol
Evening primose oil	No effect	No effect	No effect	No effect	? Decreased activity	Decreased total chol; decreased LDL (chol); ? change HDL (chol)
Reduction of dietary fat	Decreased	No effect	?	No effect	Decreased bioactivity	Decreased HDL
Norethisterone	No effect	Decreased	No effect	Decreased	Increased	Decreased HDL; increased LDL

* Bellergal probably has similar effects, †premenopausal women; chol, cholesterol

this effect was seen in two of three studies only[32,41,43]. The effect of danazol on serum lipids has been reported by several investigators[45,47–52]. Danazol consistently reduces serum HDL, (HDL_2 and HDL_3) levels by approximately 45 per cent and results in a minor increase in LDL[47–52]. Total cholesterol concentrations tend to be slightly increased when danazol is administered[47,48,51,52] whereas total triglyceride concentration remains constant[47,49,51]. The HDL:LDL ratio is markedly decreased in women receiving danazol. Danazol also reduces lecithin:cholesterol acyl transferase activity and is believed to reduce hepatic lipase activity[52].

Tamoxifen, an anti-oestrogen, reduces oestrogen activity by blocking oestrogen receptors. In normal premenopausal women it has little effect on progesterone, LH or FSH. It reduces serum prolactin, in keeping with an antagonistic role of tamoxifen in the feedback mechanism of oestrogen on pituitary prolactin release[53]. The effects of tamoxifen on serum lipids are less well documented. A significant decrease in serum cholesterol and in LDL cholesterol was seen in women receiving tamoxifen as adjuvant therapy for breast cancer[54]. This was associated with a non-significant decrease in HDL cholesterol and a non-significant increase in serum triglycerides. In another report, women with metastatic breast cancer (who may have altered dietary practices or lipoprotein metabolism as a result of their disease) experienced no significant changes in either LDL or HDL when tamoxifen was administered[55].

Evening primrose oil is an essential fatty acid supplement which contains *cis*-linoleic acid and γ-linolenic acid. Its mechanism of action is poorly documented; however, it is believed to act as a precursor of prostaglandin synthesis resulting in an increase in some prostaglandins, notably PGE_1[56]. PGE_1 is believed to decrease prolactin activity, possibly by inhibiting its action peripherally[57] The effect of evening primrose oil on serum lipids in healthy individuals is not well described[58]. It has been reported to decrease total serum cholesterol, as well as LDL cholesterol, with no associated change in HDL cholesterol in individuals with atopic eczema[59]. In the same study, a non-significant increase in HDL triglycerides was seen which was not associated with changes in either total triglycerides or LDL triglycerides A second study also found a decrease in serum cholesterol when evening primrose oil was administered to a heterogeneous group of patients[60]. The cholesterol-lowering effect was attributed to changes in LDL cholesterol. Further investigation is needed to confirm these findings and to identify the effects of evening primrose oil on serum lipids in normal individuals.

Norethisterone is a synthetic progesterone derived from 17α-ethinyl-testosterone which has mild androgenic properties. It decreases serum LH, FSH and progesterone but has no effect on oestrogen or testosterone levels[6]. It was reported to increase serum prolactin levels in the same study. It differs in its effects on plasma lipids from purely progestational agents such as progesterone and dydrogesterone, which were ineffective in relieving cyclical breast symptoms[61]. Norethisterone acts to decrease plasma HDL, particularly the HDL_2 fraction, and it increases LDL[61,62]. Purely progestational agents exert an opposite effect: that is, LDL is decreased and HDL is increased[61]. It is interesting to note that lynoestrenol, a progestational agent that was effective in improving breast abnormalities measured clinically and thermographically in women with mastodynia[36], appears to have an effect on serum lipids which is similar to that of danazol and norethisterone[47].

In an uncontrolled study, reduction of dietary fat intake from 35 per cent of caloric intake to 21 per cent of caloric intake in women with cyclical mastopathy and cystic breast disease has been reported to reduce luteal phase total oestrogens, oestrone and oestradiol significantly without changing progesterone, LH and FSH[63]. In addition, a significant reduction in bioactive lactogenic hormone (prolactin plus growth hormone) was seen which was not associated with significant changes in prolactin or growth hormone levels as measured by radioimmunoassay[64]. It was concluded that elevations in bioassayable prolactin in women with cyclical mastopathy were reversed by dietary fat reduction. Dietary fat reduction has been reported to result in a decrease in HDL cholesterol[65] although this decrease did not reach statistical significance in the small group of patients studied.

In summary, the agents that were classified as either definitely effective or possibly effective in relieving the symptoms of cyclical mastopathy exerted significant effects on serum prolactin levels and/or lipid metabolism. The most consistent effect on serum prolactin was a reduction in serum levels although the effects of norethisterone on prolactin were at variance with this result. The most consistent effect on lipid metabolism was a reduction in HDL levels; however, evening primrose oil may have exerted a different effect. Further investigation is needed to resolve apparently conflicting reports of the effects of some of these agents on prolactin and lipids, and to investigate effects that have not previously been reported. No consistent effects on sex hormones or gonadotrophins were demonstrated and it appears that these hormones may not have a major role in the pathophysiology of cyclical mastopathy.

Discussion

The results of this critical appraisal suggest that abnormalities in lipid metabolism, possibly mediated by prolactin, form the pathophysiological basis of cyclical mastopathy The role of prolactin in lipid metabolism is incompletely understood, although limited evidence is available, particularly from studies in animal models. that suggests it plays an important part. This evidence is outlined below.

In rats, the activity of lipoprotein lipase, an enzyme that is responsible for the release of lipids from lipoprotein molecules and their uptake into cells, increases in mammary tissue and decreases in peripheral adipose tissue during lactation[66] At the same time, the concentrations of non-esterified fatty acids and glycerol increase in peripheral adipose cells and, when these cells are incubated *in vitro*, there is increased release of these non-esterified fatty acids from the cells[67]. These changes are reversed when lactation ceases and are in keeping with a mobilization of fat reserves during lactation, with diversion of lipids from storage in adipose tissue to the mammary gland for milk formation.

The role of prolactin in these changes in lipid metabolism was addressed in another study in which lactating rats underwent hypophysectomy and were then given replacement hormones, including bovine prolactin, and lipoprotein lipase activity in the mammary gland and parametrial adipose tissue was measured[68]. Before hypophysectomy, lactation increased lipoprotein lipase activity in mammary tissue sixfold and reduced it in adipose tissue by more than 75 per cent Removal of the pituitary gland after the onset of lactation reversed these effects, lipoprotein lipase activities being similar to those seen in non-lactating rats When prolactin was administered to these hypophysectomized lactating animals, the pattern of lipoprotein lipase activity reverted to that seen in normal lactating rats, an effect that was best seen when prolactin was administered early in the postoperative period. It was concluded that prolactin was responsible for inducing and maintaining the pattern of activity of lipoprotein lipase seen during lactation. This pattern of activity permits increased uptake of serum lipids (in particular, triglycerides) by the mammary tissue during lactation. The administration of other hormones did not alter these effects.

Thus, it appears that prolactin may alter lipid metabolism by causing a diversion of lipids, particularly fatty acids, from peripheral adipose tissue to the mammary gland. Agents that lower prolactin would be expected to reverse this effect. Evidence relating to this effect is found in the study of women with galactorrhoea and elevated serum prolactin levels cited earlier[39]. Administration of bromocriptine to these women resulted in a fall in serum prolactin and was associated with highly significant decreases in total lipids, cholesterol and triglycerides in the mammary secretions. This was associated with reductions in fasting serum total lipids, total cholesterol, triglycerides and free fatty acids, although only the changes in total lipids and cholesterol reached statistical significance. In the same study, comparison of galactorrhoeic patients with normal lactating women demonstrated that the hyperprolactinaemic patients had significantly increased fasting total serum lipids, total cholesterol and triglycerides in addition to increased levels of these lipids in mammary secretions. These results are in keeping with the reversal of a shunt of lipids from peripheral adipose tissues to the breast in women with elevated prolactin levels, and suggests that prolactin affects lipid metabolism in adipose tissue as well as in the mammary gland.

Therefore, it appears reasonable to hypothesize that an abnormality of lipid metabolism forms the underlying pathophysiological basis for cyclical mastopathy and that those agents shown to be effective alter lipid metabolism, either directly or indirectly through an effect on prolactin. The precise nature of the abnormality of lipid metabolism involved in the pathogenesis of cyclical mastopathy is not clear; however, one could postulate that delivery to the breast of specific lipid fractions or of compounds carried by these lipid fractions is abnormal. It is known that fatty acids exert a direct effect on rat mammary cells in culture[69] and it is possible that certain fatty acids or cholesterol-containing compounds in certain lipoprotein fractions are responsible for the symptoms. Further investigation is needed to identify the specific changes in lipid metabolism that occur with each of the effective therapies and to determine whether women with cyclical mastopathy have identifiable abnormalities in lipoprotein metabolism which are reversed by these therapies.

If abnormalities of lipid metabolism are responsible for the pathophysiology of cyclical mastopathy, one should be able to demonstrate cyclical changes in lipid metabolism in relation to the menstrual cycle because the symptoms occur in a cyclical fashion. Cyclical variation of serum cholesterol, triglycerides, and lipoprotein fractions during the menstrual cycle has been described. In healthy women, total serum cholesterol and triglycerides were decreased 9 days after mid-cycle, the time at which symptoms of cyclical mastopathy are greatest in one study[70] and total cholesterol, LDL-cholesterol, and LDL-apoB (the carrier protein in the LDL fraction) were decreased during the luteal phase of the cycle in a second study[71]. In the latter study, there was a non-significant rise in HDL-cholesterol during the luteal phase of the cycle which was associated with a significant rise in the HDL:LDL ratio at the same time. In a third study[72] serum HDL was highest during ovulation and immediately afterwards. These findings demonstrate that there are cyclical variations in serum lipoproteins during the menstrual cycle in normal women, with a significant increase in the HDL:LDL ratio at the time that symptoms of cyclical mastopathy are maximum. Extrapolation of these results to women with cyclical mastopathy should be made cautiously as lipoprotein patterns in these women are not well described. Further investigation in this area is needed to determine whether women with cyclical mastopathy exhibit variations in serum lipids in relation to the menstrual cycle and whether changes occur when effective therapies are administered.

Support exists in the epidemiological literature for the hypothesis that cyclical mastopathy is a disorder of lipid metabolism. Cyclical breast symptoms are common in Western society where dietary fat intake is high[1], but are less common in Oriental societies, where fat intake is low. As noted above, reduction of the high levels of fat intake common in Western society effectively reduces the symptoms of cyclical mastopathy. In addition, other breast abnormalities such as benign breast disease characterized by histological evidence of epithelial hyperplasia are more common in Western society than among Oriental women[73] and it appears that the development of breast cancer may be related to high levels of dietary fat intake. The evidence in support of the latter association is stronger in animal models than in humans but, when the relationship is studied across large ranges of fat intake in international studies, a significant association between dietary fat and breast cancer risk is consistently demonstrated in humans[74]. While the relationship of cyclical mastopathy to these other disorders is at present unknown, their common association with diet provides general support for a role for lipids in the pathophysiology of breast disease.

Thus, this critical appraisal has identified several therapies which are effective in relieving the symptoms of cyclical mastopathy, each of which exerts an effect on lipid metabolism, serum prolactin, or both. Serum prolactin has been shown to affect lipid metabolism in rats and in women with galactorrhoea and may exert a similar effect in women with cyclical mastopathy. It is postulated that the pathophysiological basis of cyclical mastopathy may be a disorder of lipid metabolism, although there is insufficient evidence to identify the precise nature of this disorder. The cyclical nature of the symptoms may be attributable to superimposition of the normal cyclical variations in lipid metabolism that have been reported to occur during the menstrual cycle on the underlying lipid disorder. Further investigation is needed to test this hypothesis, to identify the precise nature of the lipid abnormality in this syndrome and to identify the precise effects of the effective therapies on lipid metabolism.

References

1 Wood NF, Most A, Dery GK Prevalence of premenstrual symptoms. *Am J Pub Health* 1982; **72**: 1257–64.

2. Mansel R. Breast pain. clinical spectrum and practical management. In. Forbes JF, ed. *Clinical Surgery International 10. Breast Disease*. Edinburgh: Churchill Livingstone, 1986. 48–58

3. Graham JJ, Harding PE, Wise PH, Berriman H. Prolactin suppression in the treatment of premenstrual syndrome. *Med J Aust* 1978; 18–20 (suppl)

4 Elsner GW, Buster JE, Schlinder RA, Nessim SA, Abraham GE. Bromocriptine in the treatment of premenstrual syndrome. *Obstet Gynecol* 1980, **56**: 723–6.

5. Andersen AN, Larsen JF, Steenstrup OR, Svendstrup B, Nielsen J. Effect of bromocriptine on the premenstrual syndrome A double blind clinical trial *Br J Obstet Gynaecol* 1977; **84**· 370–4

6. Ylostalo P, Kauppila J, Puolakka J, Ronnberg L, Janne O. Bromocriptine and norethisterone in the treatment of premenstrual syndrome. *Obstet Gynecol* 1982, **59**: 292–8.

7. Haspels AA. A double-blind, placebo-controlled, multicentre study of the efficacy of dydgrogesterone (Duphaston). In Vankeep PA, ed *Premenstrual syndrome* Lancaster: MTP Press, 1981: 81–92.

8. Wood C, Jakubowicz D The treatment of premenstrual symptoms with mefenamic acid. *Br J Obstet Gynaecol* 1980; **87**: 627–30.

9. Gunston KD. Premenstrual syndrome in Capetown. Part II. A double-blind placebo-controlled study of the efficacy of mefenamic acid. *S Afr J Med* 1986; **70**: 159–60.

10. Werch A, Kane RE. Treatment of premenstrual tension with metolazone. a double-blind evaluation of a new diuretic. *Curr Ther Res* 1976; **19**· 565–72.

11. Carstairs MW, Talbot DJ A placebo controlled trial of Tenavoid in the management of the premenstrual syndrome. *Br J Clin Pract* 1981, **35**: 403–9

12. Robinson K, Huntington KM, Wallace MG. Treatment of the premenstrual syndrome. *Br J Obstet Gynaecol* 1977, **84**: 784–8.

13. Boyd NF, McGuire V, Shannon P, Kriukov V, Tritchler D. A clinical trial of a low fat, high carbohydrate diet in patients with cyclical mastalgia *Breast Cancer Res Treat* 1987, **10**. 117 (abstract).

14 Boyd NF, McGuire V, Shannon P, Mahoney L, Fish E, Lickley L A randomized trial of a low fat, high carbohydrate diet in patients with cyclical mastopathy. *Lancet* 1988 (in press).

15. Mansel RE, Preece PE, Hughes LE. A double-blind trial of the prolactin inhibitor bromocriptine in painful benign breast disease. *Br J Surg* 1978; **65** 724–7

16 Hinton CP, Bishop HM, Holliday HW, Doyle PJ, Blamey RW. A double-blind controlled trial of danazol and bromocriptine in the management of severe cyclical breast pain. *Br J Clin Pract* 1986; **40**: 326–30.

17. Blichert-Toft M, Nyobe Andersen AN, Hendriksen OB, Mygind T. Treatment of mastalgia with bromocriptine. a double-blind cross-over study *Br Med J* 1979; **i**: 237.

18. Durning P, Sellwood RA. Bromocriptine in severe cyclical breast pain. *Br J Surg* 1982; **69**. 248–9.

19. Mansel RE, Wisbey JR, Hughes LE. Controlled trial of the antigonadotrophin danazol in painful nodular benign breast disease. *Lancet* 1982; **i**. 928–30

20 Doberl A, Tobiassen T, Rasussen T. Treatment of recurrent cyclical mastodynia in patients with fibrocystic breast disease. *Acta Obstet Gynecol Scand* 1984; **123** (Suppl): 177–84

21. Mansel RE, Wiseby JR, Hughes L. The use of danazol in the treatment of painful benign breast disease: Preliminary results. *Postgrad Med J* 1979; **5** (Suppl): 61–5.

22. Preece PE, Hanslip JI, Gilbert L *et al* Evening primrose oil (Efamol) for mastalgia. In: Horrobin DF, ed. *Clinical Uses of Essential Fatty Acids*. Montreal: Eden Press, 1982: 147–54.

23. Fentiman IS, Caleffi M, Brame K, Chaudary MA, Hayward JL. Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; **i**: 287–288.

24. Andersch B, Hahn L. Bromocriptine and premenstrual tension: a clinical and hormonal study *Pharmatherapeutica* 1982; **3**: 107–13.

25. Kullander S, Svanberg L. Bromocriptine treatment of the premenstrual syndrome *Acta Obstet Gynecol Scand* 1979; **58**: 375–8.

26. Watts JF, Logan Edwards RL, Butt WR. Treatment of the premenstrual syndrome using danazol. Preliminary report of a placebo-controlled, double-blind, dose ranging study. *J Int Med Res* 1985; **13**: 127–8.

27. Gilmore DH, Hawthorn RJS, McKay Hart D. Danol for premenstrual syndrome: A preliminary report of a placebo-controlled double-blind study. *J Int Med Res* 1985; **13**: 129–30.

28. Puolakka J, Makarainen L, Viinikka L, Ylikorkala O. Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors *J Reprod Med* 1985, **30**: 149–53.

29 Dennerstein L, Spencer-Gardner C, Gotts G, Brown JB, Smith MA, Burrows GD. Progesterone and the premenstrual syndrome A double-blind cross-over trial. *Lancet* 1985; **i**: 1617–21.

30 Andersch B, Hahn L. Progesterone treatment of premenstrual tension—A double blind study. *J Psychosom Res* 1985; **29**: 489–93.

31. Gorins A, Perret F, Tournant B, Rogier C, Lipszyc J. A French double-blind crossover study (Danazol versus Placebo) in the treatment of severe fibrocystic breast disease *Eur J Gynaecol Oncol* 1984, **5**: 85–9

32. Dhont M, Delbeke L, Van Eyck J, Voorhoof L. Danazol treatment of chronic cystic mastopathy: a clinical and hormonal evaluation. *Postgrad Med J* 1979, **55** (Suppl). 66–70.

33. Ernster VL, Goodson WH, Hunt TK, Petrakis NL, Sickle A, Mike R. Vitamin E and benign breast 'disease'. A double-blind, randomized clinical trial. *Surgery* 1985; **97** 490–4.

34. London RS, Sundaram GS, Murphy L, Manimekalai S, Reynolds M, Goldstein PJ. The effect of vitamin E on mammary dysplasia: A double-blind study *Obstet Gynecol* 1985; **65**: 104–6.

35 Ernster VL, Mason L, Goodson WH *et al*. Effects of a caffeine-free diet on benign breast disease: A randomized trial. *Surgery* 1982, **91**: 263–7.

36 Colin C, Gaspard U, Lambotte R. Relationship of mastodynia with its endocrine environment and treatment in a double blind trial with lynestrenol. *Arch Gynakol* 1978, **225**: 7–13.

37 Barbieri RL, Ryan KJ. Bromocriptine: endocrine pharmacology and therapeutic applications *Fertil Steril* 1983; **39**: 727–41.

38. Andersch B, Abrahamsson L, Wendestam C, Ohman R, Hahn L. Hormone profile in premenstrual tension: effects of bromocriptine and diuretics. *Chim Endo* 1979; **11**. 657–64

39 Kandau S, Gopalakrishnan V, Govindarajulu P, Indira R, Malathi T Role of prolactin in human milk composition and serum lipids studied during suppression of galactorrhea with bromocriptine *Hormone Res* 1983; **17** 93–102.

40. Dmowski WP, Headley S, Radwanska E Effects of danazol on pulsatile gonadotropin patterns and on serum estradiol levels in normally cycling women. *Fertil Steril* 1983; **39**: 49–55.

41. Guoth J, Olajos F, Zsolnai B. Endocrine consequences of danazol treatment in menorrhagia *Eur J Obstet Gynecol Reprod Biol* 1986, **23**. 79–83.

42 Peters F, Rack G, Zimmermann G, Breckwoldt M. The effect of danazol on the pituitary function, thyroid function and mastodynia. *Arch Gynakol* 1980, **230** 3–8.

43 Andrews MC, Wentz AC. The effects of danazol on gonadotropins and steroid blood levels in normal and anovulatory women. *Am J Obstet Gynecol* 1975; **121** 817–28

44. Braun P, Wildt L, Leyendeckers G. The effect of danazol on gondotropin secretion during the follicular phase of the menstrual cycle *Fertil Steril* 1983; **40**: 37–44.

45. Lawell CB, Rannevik G. A comparison of plasma protein changes induced by danazol, pregnancy and estrogens. *J Clin Endocrinol Metab* 1979; **49**: 719–25.

46 Wynn V. Metabolic effects of danazol therapy. *J Int Med Res* 1977; **5** (Suppl): 25–35.

47 Malkonen M, Manninen V, Hirvoneu E. Effects of danazol and lynestrenol on serum lipoproteins in endometriosis *Clin Pharmacol Ther* 1980; **28**: 602–8.

48. Allen JK, Fraser IS. Cholesterol light density lipoprotein and danazol. *J Clin Endrocinol Metab* 1981; **53** 149–52.

49. Luciano AA, Wallace RB, Sherman BM. Effect of danazol on plasma lipid and lipoprotein levels in normal women. *Atherosclerosis* 1982; **43**: 133–7.

50. Luciano AA, Hauser KS, Chaples FK, Davis WA, Wallace RB Effects of danazol on plasma lipid and lipoprotein levels in healthy women and in women with endometriosis. *Am J Obstet Gynecol* 1983; **145** 422–6.

51. Schwepe KW, Assmann G. Changes of plasma lipids and lipoprotein levels during danazol treatment for endometriosis. *Horm Metab Res* 1984; **16**: 593–7.

52. Fahraeus L, Larsson-Cohn U, Ljungberg S, Wallentin L Profound alterations of the lipoprotein metabolism during danazol treatment in premenopausal women *Fertil Steril* 1984; **42**: 52–7.

53. Heel RC, Brogden RN, Speight TM, Avery GS. Tamoxifen: A review of pharmacological properties and therapeutic use in the treatment of breast cancer *Drugs* 1978, **16**: 1–24.

54. Rossner S, Wallgren A. Serum lipoproteins and proteins after breast cancer surgery and effects of tamoxifen. *Atherosclerosis* 1984, **52**: 339–46.

55. Wander HE, Teichmann AT, Cremer P *et al.* Changes in serum-lipoproteins under tamoxifen (T), medroxy progesterone acetate (MPA) and amino-glutethimide (AG) with regard to adjuvant hormone therapy of breast cancer. *Second International Symposium on Anti-hormones in Breast Cancer, Berlin* ICI Pharmaceuticals Division, 1984: 55 (abstract)

56 Horrobin DF. Essential fatty acids: A review. In: Horrobin DF, ed *Clinical Uses of Essential Fatty Acids*. Montreal: Eden Press, 1982: 3–36.

57. Horrobin DF. Cellular basis of prolactin action. *Med Hypotheses* 1979; **5**: 599–620.

58. Lowndes RH, Mansel RE. The effects of evening primrose oil administration on the serum lipids of normal and obese human subjects. In: Horrobin DF, ed. *Clinical Uses of Essential Fatty Acids*. Montreal: Eden Press, 1982. 37–52.

59. Wright S, Burton JL. A placebo controlled trial of the effect of efamol (evening primrose oil) on atopic eczema and blood lipids In: Horrobin DF, ed *Clinical Uses of Essential Fatty Acids* Montreal: Eden Press: 1982: 73–9.

60. Horrobin DF, ed. The lowering of plasma cholesterol levels by essential fatty acids. In: *Clinical Uses of Essential Fatty Acids*. Montreal: Eden Press, 1982: 89–96

61. Fahraeus L, Larsson-Cohn U, Wallentin L. L-Norgestrel and progesterone have different influences on plasma lipoprotein changes. *Acta Obstet Gynecol Scand* 1982; **105** (Suppl): 33–6.

62. Wingrave SJ. Progestogen effects and their relationship to lipoprotein changes. *Acta Obstet Gynecol Scand* 1982; **105** (Suppl): 33–6

63. Rose DP, Boyar AP, Cohen C, Strong LE Effect of a low fat diet on hormone levels in women with cystic breast disease. I. Serum steroids and gonadotropins. *J Natl Cancer Inst* 1987, **78** 623–6.

64. Rose DP, Cohen LA, Beske B, Boyar AP. Effect of a low fat diet on hormone levels in women with cystic breast disease. II Serum radioimmunoassayable prolactin and growth hormone and bioactive lactogenic hormone. *J Natl Cancer Inst* 1987, **78**: 624–31.

65. Lee-Han H, Cousins M, Beaton M *et al* Measurement of compliance in a randomized trial of dietary fat reduction in patients with breast dysplasia: relationship between nutrients and plasma lipids. *Am J Clin Nutr* 1988, **48** 575–86.

66. Hamosh M, Clary TR, Chernick SS, Scow RO Lipoprotein lipase activity of adipose and mammary tissue and plasma triglyceride in pregnant and lactating rats *Biochim Biophys Acta* 1970; **210**:

473–82.
67 Smith RW, Walsh A. Effect of lactation on lipolysis in rat adipose tissue. *Lipids* 1976; **11**: 418–20.
68. Zinder O, Hamosh M, Fleck TR, Scow RO Effect of prolactin on lipopoprotein lipase in mammary gland and adipose tissue of rats. *Am J Physiol* 1974; **226**: 744–8
69. Wicha MS, Liotta LA, Kidwel WR. Effects of free fatty acids on the growth of normal and neoplastic rat mammary epithelial cells. *Cancer Res* 1979, **34**: 426–35.
70. Low-Beer TS, Wicks ACB, Heaton KW, Durrington P, Yeates J. Fluctuation of serum and bile lipid concentrations during the menstrual cycle. *Br Med J* 1977; **i**: 1568–70.
71. Kim HJ, Kalkhoft RK. Changes in lipoprotein composition during the menstrual cycle. *Metabolism* 1979; **28**: 663–8
72. Krauss RM, Lindgren FT, Wingard J, Bradley DD, Ramcharan S Effects of estrogens and progestins on high density lipoproteins. *Lipids* 1979; **14**: 113–8.
73. Sasano N, Tateno H, Stemmermann GN. Volume and hyperplastic lesions of breasts of Japanese women in Hawaii and Japan. *Prev Med* 1978; **7**: 196–204.
74. Goodwin PJ, Boyd NF. Critical appraisal of the evidence that dietary fat intake is related to breast cancer risk in humans *J Natl Cancer Inst* 1987; **79** 473–85.

Paper accepted 12 May 1988

Br. J. Surg. 1988, Vol. 75, September, 845–846

Dosage and duration of tamoxifen treatment for mastalgia: a controlled trial

A controlled trial has been conducted in which 60 women with mastalgia were randomly allocated to receive tamoxifen at a dosage of either 10 mg or 20 mg daily for either 3 or 6 months. All eligible patients had self-rated moderate or severe mastalgia present for at least 6 months, for which no specific therapy had been given for the previous 3 months. End points of the study were pain control, measured by linear analogue scales, relapse rate and side-effects. Pain relief was achieved in 90 per cent of those receiving 10 mg daily and 86 per cent of those given 20 mg daily. The relapse rate was also similar for both dosages, being 48 per cent and 39 per cent respectively and usually occurred within 2–3 months of discontinuing treatment. However, side-effects were reported less frequently among those receiving 10 mg daily (21 per cent versus *64 per cent;* $\chi^2 = 11{\cdot}1$, $P < 0{\cdot}001$*). Prolongation of treatment from 3 months to 6 months did not materially improve the response rate (85 per cent* versus *90 per cent). Side-effects were similar, as was the relapse rate among the patients receiving the two durations of treatment. The agent proved to be significantly more effective in the relief of cyclical rather than non-cyclical pain (94 per cent* versus *56 per cent). Use of tamoxifen for the treatment of mastalgia is still experimental. Nevertheless, for the majority of women with mastalgia, pain relief can be achieved using tamoxifen 10 mg daily, given for a 3-month course. As almost half these patients will develop relapse of breast pain it may be necessary to give longer courses of therapy, although the safety of this more protracted treatment has yet to be determined.*

Keywords: Tamoxifen, mastalgia

I. S. Fentiman,
M. Caleffi,
H. Hamed and
M. A. Chaudary

ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, UK

Correspondence to: Mr I. S. Fentiman

Breast pain can be a worrying symptom for some patients, who may fear that this is due to underlying malignancy. This is rarely the case[1], and after clinical and possibly radiological exclusion of cancer and reassurance of the patients the pain resolves spontaneously in the majority of cases. Nevertheless, hormonal treatment may be required for those women with prolonged severe pain. Until recently the most commonly used effective agents were danazol and bromocriptine. In a recent double-blind placebo-controlled trial carried out at Guy's Hospital, it was shown that tamoxifen relieved breast pain in approximately 70 per cent of cases[2]. In this trial tamoxifen 20 mg daily was given for 3 months. Although the treatment was effective, there was a fairly high rate of subsequent recurrence of pain[3]. In addition, some patients complained of side-effects including menstrual irregularity, hot flushes, nausea and bloating.

For these reasons a second trial was designed with two major aims. First, the study addressed the question of the appropriate dose of tamoxifen. By reducing the dosage to 10 mg daily, could the incidence of side-effects be reduced without prejudicing the effectiveness of treatment? Secondly, if the duration of treatment was extended to 6 rather than 3 months, could the rate of pain control be improved and the subsequent relapse rate be reduced?

To answer these questions, a trial of factorial design was conducted in which patients were randomly allocated to receive either tamoxifen 10 mg or 20 mg daily for either 3 or 6 months.

Patients and methods

Patients

To be eligible for the trial, patients were aged 20–50 years and had either cyclical or non-cyclical breast pain This was self-rated as either moderate or severe and had been present for at least 6 months None of the patients had received any specific treatment for breast pain within the 3 months before entry to the trial For 6 weeks before entry, patients were asked to record the severity of their pain on 10 cm linear analogue score cards, which were also completed while on treatment None had breast lesions requiring biopsy which were excluded by clinical examination Mammography was performed in those aged over 35 years.

Randomization

On entry to the trial patients were randomly allocated to receive tamoxifen either 10mg or 20mg daily. Neither the patient nor the doctor knew the dosage. In addition, patients were randomly allocated to receive treatment for either 3 or 6 months Both patient and doctor were aware of the assigned duration of treatment. Tamoxifen tablets were removed from the blister pack by the pharmacist and dispensed in a light-proof container.

Assessment

Patients were seen at 4 weeks, 12 weeks and 24 weeks, and 1 year At each visit a clinical examination was performed and an assessment was made of tenderness and nodularity on a 1–3-point scale (1, no nodularity; 2, some nodularity; 3, marked nodularity, similarly for tenderness: 1, no tenderness; 2, some tenderness, 3, marked tenderness) Patients were asked about side-effects and linear analogue cards were collected As in the previous trial, treatment success was recorded when there was a greater than 50 per cent reduction in the mean pain score for each 4 weeks of treatment compared with the 6-week pretreatment period.

Results

The study started in February 1986 and comprised 60 patients with a median follow-up at the time of review of 17 months. A comparison of the patients in the different treatment groups is given in *Table 1* which shows no major differences between

0007-1323/88/090845-02$3 00

Table 1 *Comparison of clinical features of patients receiving different dosages and durations of tamoxifen treatment*

	Dosage		Duration	
	10 mg	20 mg	3 months	6 months
Number	29	28	27	30
Age (mean ± s.e.m.)	37·0 ± 1·3	38·2 ± 1·6	38·7 ± 1·7	36·6 ± 1·3
Menstruating	26 (90%)	21 (75%)	20 (74%)	27 (90%)
Hysterectomy	3 (10%)	7 (25%)	7 (26%)	3 (10%)
Duration of symptoms in months (mean ± s.e.m.)	30 ± 4	27 ± 3	30 ± 4	26 ± 3
Cyclical pain	24 (83%)	24 (86%)	23 (85%)	25 (83%)

Table 2 *Results of treatment*

Dosage (mg)	Duration (months)	Number	Response	Side-effects	Relapse
10	3	14	12/14 (86)	3/14 (21)	6/14 (43)
10	6	15	14/15 (93)	3/15 (20)	8/15 (53)
20	3	13	11/13 (85)	8/13 (62)	6/13 (46)
20	6	15	13/15 (87)	10/15 (67)	5/15 (33)

Percentages in parentheses

Table 3 *Side-effects of tamoxifen therapy*

Side-effects	Tamoxifen 10 mg	Tamoxifen 20 mg
Hot flushes	2 (7)	10 (36)
Irregular cycle/amenorrhoea	3 (10)	7 (25)
Weight gain	0	2 (7)
Nausea	1 (3)	1 (4)
Vaginal dryness	0	1 (4)
Bloating	0	1 (4)

Percentages in parentheses

the clinical characteristics of the women randomly allocated to the four treatment groups. Three patients were excluded from the analysis, one because of pregnancy before she started therapy, and two who did not attend for follow-up. Response to treatment, side-effects and relapse rate are shown in *Table 2*. For patients receiving tamoxifen 10 mg daily the overall pain response rate was 26/29 (90 per cent) compared with 24/28 (86 per cent) for those receiving 20 mg daily ($\chi^2 = 0{\cdot}21$; not significant).

Relapse of breast pain after discontinuation of treatment occurred in 14/29 (48 per cent) of those who had received 10 mg daily and 11/28 (39 per cent) of those given 20 mg daily ($\chi^2 = 0{\cdot}47$, not significant). Of those patients relapsing, the median pain-free interval from the end of treatment was 3 months for those that had received either 10 mg or 20 mg tamoxifen.

Increasing the duration of treatment from 3 months to 6 months did not produce a significant increase in response rate, which was 23/27 (85 per cent) compared with 27/30 (90 per cent) ($\chi^2 = 0{\cdot}51$, not significant). There was a progressive increase in response up to 12 weeks but no additional responses after this time. Pain relief was achieved in 26 (52 per cent) at 4 weeks, 39 (78 per cent) at 8 weeks and 50 (100 per cent) at 12 weeks. This pain relief was similarly manifested as a diminution of tenderness on the simple scale but without any alteration in nodularity score. There was no significant increase in side-effects, which were reported by 11/27 (41 per cent) of those treated for 3 months and 13/30 (43 per cent) of those given 6 months of tamoxifen. Relapse rates were similar after 3 and 6 months, being 12/27 (44 per cent) and 13/30 (43 per cent) respectively.

Side-effects were reported more frequently by patients receiving the higher dose of 20 mg daily: 18/28 (64 per cent) *versus* 6/29 (21 per cent). This difference was statistically significant ($\chi^2 = 11{\cdot}1$, $P < 0{\cdot}001$). The side-effects reported by the patients are detailed in *Table 3*. When patients complained of more than one side-effect these have been recorded separately. The most common problem was hot flushes which were usually reported by older women, closer to their natural menopause. Four patients, all aged over 35 years, developed amenorrhoea. In one patient, nausea was so severe that she discontinued her treatment.

The breast pain was cyclical in 48/57 (84 per cent) and non-cyclical in 9/57 (16 per cent). Pain was relieved by tamoxifen in 45/48 (94 per cent) of the cyclical group and 5/9 (56 per cent) of those with non-cyclical symptoms (χ^2 (Yates) = $7{\cdot}2$; $P < 0{\cdot}001$).

Discussion

This factorial design study sought to define the most effective tamoxifen regimen for the management of mastalgia. With regards to the most appropriate dosage, it does appear that a similar rate of pain relief was achieved with either 10 mg or 20 mg daily, but the former dose was associated with significantly fewer side-effects. Prolongation of duration of treatment did not achieve significantly greater rates of pain relief and there was a similar incidence of side-effects. A significantly better response rate was observed in patients with cyclical rather than non-cyclical breast pain.

However, it does appear that although tamoxifen is effective in relieving mastalgia, the underlying undefined endocrine abnormality is only suppressed by the treatment. Thus, just under one-half of the patients developed subsequent relapse after discontinuation of tamoxifen therapy. This, therefore, may be a reason for giving more prolonged therapy for possibly 12 months. One treatment strategy would be to give a trial course of tamoxifen 10 mg for 3 months. Those patients relapsing after discontinuation would then be given a further 9 months of treatment. However, it should be stressed that the long-term safety of tamoxifen administration in premenopausal women, without malignancy, has yet to be determined. Possible secondary effects of tamoxifen on bone mineral content and high density lipoprotein metabolism have been investigated as part of this study and will be reported subsequently. Recently it has been found that high dosages of tamoxifen produce hepatocellular carcinomas in rats (I. Jackson, personal communication), although the relevance of this to humans has not yet been determined[4]. Although tamoxifen is effective in relieving mastalgia, its use must still be regarded as experimental and administration should at present be confined to patients who have been fully investigated and who are under the supervision of a breast clinic.

References

1. Preece PE, Baum M, Mansel RE *et al.* Importance of mastalgia in operable breast cancer *Br Med J* 1982; **284**: 1299–1300.
2. Fentiman IS, Caleffi M, Brame K, Chaudary MA, Hayward JL. Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; **i**. 287–8.
3. Fentiman IS. Tamoxifen and mastalgia. An emerging indication *Drugs* 1986; **32**. 477–80.
4. Fentiman IS, Powles TJ. Tamoxifen and benign breast conditions: the end or just the beginning? *Lancet* 1987; **ii**: 1070–71

Paper accepted 3 May 1988

Br. J. Surg. 1988, Vol. 75, September, 847–850

Use of fine needle aspiration cytology with immediate reporting in the diagnosis of breast disease

S. Nicholson,
J. R. C. Sainsbury,
V. Wadehra*,
G. K. Needham and
J. R. Farndon

Departments of Surgery and
**Cytopathology, University of*
Newcastle upon Tyne, UK

Correspondence to:
Mr J. R. Farndon, University
Department of Surgery, Bristol
Royal Infirmary, Bristol BS2 8HW,
UK

Fine needle aspiration biopsy for cytological examination (FNAC) is becoming increasingly accepted as a means of tissue diagnosis in breast disease. This study examines the feasibility and accuracy of FNAC in 'immediate reporting' by a consultant cytopathologist in a busy breast clinic. Over a 2-year period, 884 cytology reports were analysed. An initial clinical report and subsequent final cytological diagnosis was made. Fine needle aspiration provided adequate material for cytological evaluation in 635 of the 884 biopsies (71·6 per cent) and this proportion was greater when discrete lumps were considered (463 of 562 biopsies = 82·4 per cent). In diffuse and cystic disease, however, the adequacy of specimens was reduced: 50 per cent and 65 per cent respectively. On immediate reporting the diagnostic sensitivity for all patients was 88 per cent (discrete lumps only, 92·5 per cent) and the specificity was 99·8 per cent (discrete lumps only, 100 per cent). FNAC retains its diagnostic accuracy when immediate reporting is employed and this study demonstrates that this technique can be used in making a diagnosis in patients with breast disease.

Keywords: Breast disease, fine needle aspiration cytology, immediate reporting

Fine needle aspiration biopsy for cytology (FNAC) has been employed in the diagnosis of palpable breast disease in Newcastle upon Tyne for over 7 years. This technique is slowly gaining acceptance in the UK but doubts exist among clinicians and pathologists as to its accuracy and reliability and these reservations are greater in the USA[1]. Patients, unaware of their diagnosis pre-operatively, may still be submitted to biopsy and frozen section. The technique of FNAC has been well described previously[2,3] and its accuracy has been shown to compare favourably with clinical examination and mammography[4].

When a breast clinic was set up at the Royal Victoria Infirmary in Newcastle in 1983 the value of FNAC was extended by providing immediate reporting. The commercially available rapid stain Diff Quik† allowed a provisional report to be given within 10 min. The value and accuracy of the immediate cytological diagnosis in the patient's management is examined in this report.

Patients and methods

The breast clinic sees patients presenting with breast lumps, diffuse nodularity, breast pain and nipple discharge and inversion. All patients with palpable abnormalities are subjected to FNAC. A consultant cytopathologist (V.W.) and a technician from the cytology laboratory attend the clinic. FNAC is performed by each of three surgeons (consultant, senior registrar and senior house officer) working in the clinic. The importance of correct smear preparation has been emphasized[5]. An SHO spends only 4 months with the unit but performs the FNAC and smear preparation under strict supervision from the consultant cytopathologist. The importance of this technique in the surgical armamentarium justifies the practice of training all junior members helping in the clinic.

A 21 gauge (green cap) needle on a 20 ml syringe is mounted in a Cameco† syringe pistol holder. The use of the syringe holder greatly facilitates the biopsy by allowing maximum suction to be maintained with ease and improving directional control, ensuring more cellular specimens (*Figure 1*).

The best smear (by naked eye inspection) is selected by the cytologist, stained by the Diff Quik method[5], examined in the clinic and a provisional report issued within 10–15 min. Other slides are taken to the main cytology laboratory at the end of the clinic and stained by the May-Grünwald–Giemsa (MGG) technique. A definitive report is issued by the same cytologist within 24–48 h.

All smears (Diff Quik and MGG) are graded from 0–5 according to cytological parameters (*Table 1*) in a system similar to that used at the Royal Marsden Hospital[6] and that described by Strawbridge *et al.*[7] with the addition of the AC1 category. The AC1 smear is included in the

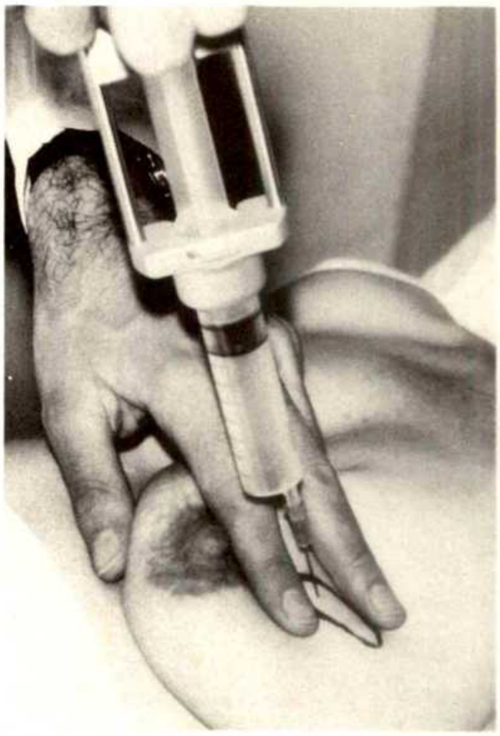


Figure 1 *Fine needle aspiration biopsy of breast in use showing advantage of syringe holding pistol*

---

† Diff Quik (Harleco American Hospital Supply Corporation, UK) and Cameco (AG Täbyvagen, Sweden) are registered trade marks

unsatisfactory group because, although they are not acellular, smears with insufficient numbers of ductal cells do not allow a confident diagnosis. They are usually obtained from diffuse benign lesions. When an unsatisfactory sample is obtained from a patient with high clinical suspicion of malignancy a repeat biopsy is performed during the same clinic visit. The results of the 'immediate' report are used to initiate discussions with the patient with regard to diagnosis and treatment. All cysts are aspirated and if the fluid is bloodstained it is examined cytologically but if not it is discarded[11]. If a palpable abnormality remains after cyst drainage, FNAC of the edge of the lesion is taken to ensure that a cystic carcinoma is not missed. All patients aged 35 years or older with clinically benign cystic disease are examined mammographically and are seen for follow-up at least once, usually after 3 months.

The aims of this study were to examine the accuracy and sensitivity of FNAC with immediate reporting compared with similar parameters on definitive reports. The definitions are as in *Table 2*.

Table 1 *Cytological reporting format*

Unsatisfactory	
AC0:	No ductal cells seen. Presence of striated muscle or myoepithelial cells disregarded
AC1:	Scanty ductal cells considered inadequate for diagnostic purposes
Benign	
AC2:	Adequate number of ductal cells without any atypia
AC3:	Benign breast disease with minor atypia
Malignant	
AC4:	Suspicious of malignancy including cases with scanty malignant cells and well differentiated tumours
AC5:	Unequivocal malignancy

Table 2 *Definitions*

False positive rate	$= \frac{FP}{TP+FP}$	* 100 per cent
False negative rate	$= \frac{FN}{TN+FN}$	* 100 per cent
Sensitivity	$= \frac{TP}{TP+FN}$	* 100 per cent
Specificity	$= \frac{TN}{TN+FP}$	* 100 per cent
Diagnostic accuracy	$= \frac{TP+TN}{TP+TN+FP+FN}$	* 100 per cent

FP, false positive; FN, false negative; TP, true positive; TN, true negative

Results

In 2 years 884 needle aspirates were performed on which an immediate and definitive report was given (*Table 3*). Where the cytology was malignant, confirmatory histology was obtained in all patients other than elderly, postmenopausal patients (over 70 years) who were treated by primary endocrine therapy. In patients with clinically and cytologically benign disease only a minority of lesions were excised for histological confirmation[8]. The only indications for excision in this group were requests by the patient and the uncommon finding of a clinically and cytologically diagnosed fibroadenoma which had increased in size at follow-up. All lesions with persistent AC3 grades (benign with minor to moderate atypia) were excised and four false negatives occurred in this group. AC3 lesions were, however, a small group, representing 8 per cent of lumps, 3·4 per cent of diffuse nodularity and 10 per cent of cystic disease on final reporting.

Diagnostic accuracy was consistently high for both immediate and definitive reporting with only one false positive and four 'false suspicious' reports (*Table 4*). The term 'false suspicious' requires some explanation. In this study over 95 per cent of lesions with AC4 cytology ultimately proved to be malignant. In all cases where the AC4 grade persisted (i.e. on immediate and definitive reports and repeat FNAC) a wide lumpectomy was performed, and 25 per cent of immediate AC4 reports subsequently had a definitive AC5 grade. Four patients with grade 4 cytology proved to have benign lesions on histology hence the term 'false suspicious' but because a mastectomy was never performed on a grade 4 report alone these patients did not receive inappropriate treatment. Mastectomy was occasionally performed without confirmatory open biopsy where an AC4 report was supported by an unequivocal mammogram report of malignancy.

Table 3 *Cytological diagnoses from 884 cytology reports*

	Clinical finding					
	Lump		Diffuse		Cystic	
Cytological report	Immediate	Definitive	Immediate	Definitive	Immediate	Definitive
Unsatisfactory	100 (17·8)	97 (17·2)	130 (48·9)	133 (50)	19 (33·9)	14 (25)
Benign	327 (58·2)	329 (58·5)	130 (48·9)	123 (46·2)	37 (66·1)	42 (75)
Suspicious and malignant	135 (24)	136 (24·2)	6* (2·2)	10 (3·8)	—	—

* Includes cases of impalpable malignancy noted on mammography
Figures in parentheses are percentages within each clinical group

Table 4 *Diagnostic anomalies*

	False positive		False suspicious*		False negative	
	Immediate	Definitive	Immediate	Definitive	Immediate	Definitive
Lumps	0	0	0	1	11	11
Diffuse nodularity	1†	1†	0	3	8	7
Cystic disease	0	0	0	0	0	0
All cases	1	1	0	4	19	18

* False suspicious: AC4 cytology but benign histology
† Recorded here but there was *no* palpable abnormality. Patient presented with nipple bleeding and FNAC of subareolar tissue AC5. Mammogram also suspicious. Mastectomy performed—histology non-confirmatory

Table 5 *Results expressed as percentages*

	All cases		Lumps only	
	Immediate	Definitive	Immediate	Definitive
False positive and false suspicious	0·7 (1)	3·4 (5)	0	0·7 (1)
False negative	3·8 (19)	3·6 (18)	3·3 (11)	3·3 (11)
Sensitivity	88 (140/159)	88·7 (141/159)	92·5 (135/146)	92·5 (136/147)
Specificity	99·8 (475/476)	99 (476/481)	100 (317/317)	99·7 (318/319)
Diagnostic accuracy	96·8 (615/635)	96·4 (617/640)	97·6 (452/463)	97·4 (454/466)

Unsatisfactory aspirates have been excluded from the calculation. Figures in parentheses are the actual numbers

Only one false positive occurred (*Table 4*). In *all* other patients where AC5 cytology led to surgery, subsequent histology was confirmatory and it has been the routine to proceed to mastectomy or conservative surgery on the strength of the cytology alone without confirmatory open biopsy and frozen section.

There were 19 false negative results on immediate reporting and 18 on definitive reporting. Not all these patients had discrete, palpable abnormalities. In some there was only diffuse thickening and in two patients there was no palpable tumour, the diagnosis being confirmed only after mammographic localization. To allow a one-stage procedure in these patients frozen section was used to confirm malignancy, and then mastectomy was performed.

Seven of the false negatives in both the immediate and final reporting groups, therefore, occurred in four patients in whom the diagnosis of malignancy would have been problematic for any of the currently available biopsy techniques. The results are expressed in terms of diagnostic sensitivity, specificity and overall accuracy in *Table 5*.

There were 11 instances where a change occurred in diagnostic group between immediate and definitive reporting. In eight the immediate report was benign and the definitive report suspicious of malignancy (AC4). In four of these the immediate report was incorrect (i.e. carcinoma proven on open biopsy—false negative immediate reports). In the other four cases the definitive report was in error (i.e. benign histology—false suspicious definitive reports). In the remaining three cases the immediate cytology gave a malignant diagnosis whereas the definitive report was benign. After histological examination all of these proved to be false negative for definitive reporting.

Discussion

These results demonstrate that it is possible to make an accurate immediate cytological diagnosis in patients with breast disease. In this study diagnostic accuracy was over 96 per cent for all lesions and over 97 per cent for discrete lumps only and there was no difference between immediate and definitive reporting. Sensitivity approached 90 per cent for all lesions and for discrete lumps it was 92·5 per cent. Specificity was over 99 per cent for all lesions and for immediate reporting of discrete lumps in this study was 100 per cent. There was no significant difference in any category between immediate and definitive reporting.

The overall accuracy of FNAC in the diagnosis of breast disease has been well documented[1–3,9,10]. FNAC is simple, inexpensive, well tolerated and rapid. If immediate reporting is to be used in a clinic then a cytopathologist and technician must attend, but savings in theatre, anaesthetic and routine histopathological facilities consequent upon the fall in demand for frozen sections make this practice highly cost effective. The skills required for FNA biopsy are easy to master but clinical experience is necessary to ensure that the appropriate area is biopsied. These results have shown that a higher proportion of satisfactory (diagnostic) aspirations is obtained when only discrete lumps are sampled. It is, however, an extremely valuable adjunct to the diagnosis and follow-up of patients with diffuse or cystic disease[10]. Biopsies from diffuse fibroadenosis often provide scanty or no ductal cells and are, therefore, included in the unsatisfactory biopsies. These patients are often young, give a good history of cyclical changes in their breasts and can be followed safely by clinical examination and, perhaps, mammography. No cancers have been missed in this group of patients with diffuse or cystic disease by adopting this policy. FNAC is less painful, requiring no local anaesthetic, wider ranging in its sampling and more economical than core (Tru-cut*) biopsy[1,12]. Tru-cut biopsy in most studies has been reserved for patients with a discrete palpable lump (usually larger than 2·5 cm in diameter) in whom the suspicion of malignancy is high[13,14]. One recent paper[15] recommends that Tru-cut should be used for suspicious lumps more than 1 cm in diameter and FNAC for those less than 1 cm in diameter. FNAC is accurate for lumps of all sizes providing the needle enters the lump. There is little logic in a dual biopsy policy and, in addition, the diagnosis of soft tissue recurrence of breast cancer is more efficiently made by FNAC than Tru-cut[16]. The risk of seeding tumour cells along the needle track has been associated with the use of larger cutting needles but there is essentially no danger of implantation with fine needle breast aspiration[2].

The value of FNAC as part of the diagnostic triad of clinical examination, cytology and mammography is being increasingly emphasized[17,18] but clinical examination with cytology alone is highly accurate[19] and this study emphasizes the utility of FNAC in patients with clinically suspicious lesions and in those with a low degree of suspicion who are too young for mammography.

The accuracy of FNAC compares well with that of open biopsy and frozen section which does have a documented false positive and negative risk[20–22]. Open biopsy techniques incur a definite financial cost to the Health Service and a psychological cost to the patients—at its greatest when the patient consents for 'biopsy proceeding to mastectomy if necessary'. With 'conventional' management a great many patients with benign disease experience unnecessary anxiety and surgery while patients with malignant disease may not have the benefit of a full pre-operative discussion with their surgeon on the available therapeutic options. Total reliance on open biopsy techniques would result in the overtreatment of a number of elderly postmenopausal patients who are known to benefit from primary endocrine treatment[23].

Excision of the tumour allows the measurement of biological and prognostic parameters. Non-excision does not preclude these same observations and although FNAC cannot differentiate between invasive and *in situ* carcinomas it is being applied to techniques such as oestrogen receptor analysis[24], ploidy[25] and electron microscopy[26]. Cytologically obtained prognostic markers are also under evaluation and may expand the clinical relevance of the method[27].

---

* *Tru-cut is a registered trademark*

Combined with clinical examination and mammography, FNAC with immediate reporting provides a highly accurate diagnostic method in all forms of palpable breast disease and it allows the clinician to discuss diagnosis and management with the patient at the initial clinic attendance, avoiding delay and added anxiety.

Acknowledgements

We thank Miss Anne Wood, Senior MLSO (Cytology Laboratory) for assistance with data retrieval.

References

1. Smeets HJ, Saltzstein SL, Meurer WT, Pilch YH. Needle biopsies in breast cancer diagnosis. techniques in search of an audience. *J Surg Oncol* 1986; **32**: 11–15.
2. Franzen S, Zajicek J. Aspiration biopsy in diagnosis of palpable lesions of the breast. Critical review of 3479 consecutive biopsies. *Acta Radiol Therapy Physics Biology* 1968; 7: 241–62
3. Webb AJ. The diagnostic cytology of breast carcinoma. *Br J Surg* 1970; **57**: 259–63.
4. Thomas JM, Fitzharris BM, Redding WH *et al.* Clinical examination, xeromammography, and fine-needle aspiration cytology in diagnosis of breast tumours. *Br Med J* 1978; **ii**: 1139–41.
5. Duguid HLD, Wood RAB, Irving AD, Preece PE, Cuschieri A. Needle aspiration of the breast with immediate reporting of material. *Br Med J* 1979; **ii**: 185–7.
6. Trott PA Breast cytodiagnosis. In: Sloane JP, ed. *Biopsy Pathology of the Breast*. London· Chapman and Hall, 1985: 46–63
7. Strawbridge HTG, Bassett AA, Foldes I. Role of cytology in management of lesions of the breast. *Surg Gynecol Obstet* 1981; **152**: 1–7.
8. Sainsbury JRC, Nicholson S, Needham GK, Wadehra V, Farndon JR. The natural history of the discrete benign breast lump. *Br J Surg* 1988 (in press)
9. Wanebo HJ, Feldman PS, Wilhelm MC, Covell JL, Binns RL. Fine needle aspiration cytology in lieu of open biopsy in management of primary breast cancer. *Ann Surg* 1984; **199**: 569–78.
10. Ulanow RM, Galblum L, Canter JW. Fine needle aspiration in the diagnosis and management of solid breast lesions *Am J Surg* 1984; **148**: 653–7.
11. Forrest APM, Kirkpatrick JR, Roberts MM. Needle aspiration of breast cysts. *Br Med J* 1975; **iii**: 30–31.
12. Shabot MM, Goldberg IM, Schick P, Nieberg R, Pilch YH. Aspiration cytology is superior to TRU-CUT needle biopsy in establishing the diagnosis of clinically suspicious breast masses. *Ann Surg* 1982; **196**: 122–6.
13. Fentiman IS, Millis RR, Hayward JL. Value of needle biopsy in outpatient diagnosis of breast cancer *Arch Surg* 1980; **115**: 652–3.
14. Minkowitz S, Moskowitz R, Khafif RA, Alderete MA. TRU-CUT needle biopsy of the breast. An analysis of its specificity and sensitivity *Cancer* 1986, **57**: 320–3.
15. Bradbeer JW. Outpatient diagnosis of breast cancer. *Br J Surg* 1985, **72**: 927–8.
16. Pedersen L, Guldhammer B, Kamby C, Aasted M, Rose C. Fine needle aspiration and TRU-CUT biopsy in the diagnosis of soft tissue metastases in breast cancer. *Eur J Cancer Clin Oncol* 1986; **22**: 1045–52.
17. Azzarelli A, Guzzon A, Pilotti S *et al.* Accuracy of breast cancer diagnosis by physical, radiologic and cytologic combined examinations. *Tumori* 1983; **69**; 137–41.
18. Kreuzer G, Boquoi E. Aspiration biopsy cytology, mammography and clinical exploration: a modern set up in diagnosis of tumours of the breast. *Acta Cytol* 1976; **20**: 319–23.
19. Rimsten A, Stenkvist B, Johanson H, Lindgren A. The diagnostic accuracy of palpation and fine needle aspiration and an evaluation of their combined use in the diagnosis of breast lesions. *Ann Surg* 1975; **182**: 1–8.
20. Holaday WJ, Assor D Ten thousand consecutive frozen sections. *Am J Clin Pathol* 1974; **61**: 769–77.
21. Kaufman Z, Lew S, Griffel B, Dinbar A Frozen section diagnosis in surgical pathology. A prospective analysis of 526 frozen sections. *Cancer* 1986; **57**· 377–9.
22. Rosen PP. Frozen section diagnosis of breast lesions. Recent experience with 556 consecutive biopsies. *Ann Surg* 1978; **187**: 17–19.
23. Preece PE, Wood RAB, Mackie CR, Cuschieri A. Tamoxifen as initial sole treatment of localised breast cancer in elderly women: a pilot study. *Br Med J* 1982; **284**: 869.
24. Crawford DJ, Lope-Pihie A, Cowan S, George WD, Leake RE. Pre-operative determination of oestrogen receptor status in breast cancer by immunocytochemical staining of fine needle aspirates *Br J Surg* 1985; **72**. 991–3.
25. Auer G, Tribukait B. Comparative single cell and flow DNA analysis in aspiration biopsies from breast carcinomas. *Acta Pathol Microbiol Scand* 1980; **88**: 355–8.
26. Domagala W, Koss LG. Sueface configuration of human tumour cells obtained by fine needle aspiration biopsy. *Scan Electron Microsc* 1980; 3. 101–8.
27. Mouriquand J, Pasquier D. Fine needle aspiration of breast carcinoma. a preliminary cytoprognostic study. *Acta Cytol* 1980; **24**: 153–9.

Paper accepted 13 May 1988

Br. J. Surg. 1988, Vol. 75, September, 851–853

Role of Doppler ultrasound flowmetry in the diagnosis of breast lumps

A. Srivastava, D. J. T. Webster, J. P. Woodcock*, S. Shrotria, R. E. Mansel and L. E. Hughes

*Departments of Surgery and *Bioengineering, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK*

Correspondence to.
Mr D J T Webster, Llandough Hospital, Near Penarth, Cardiff
CF6 1XX, UK

One hundred and five patients with discrete breast lumps were examined with a 10 MHz Doppler ultrasonic flowmeter. Doppler flow signals were analysed on an Angioscan spectrum analyser. Recordings from the opposite normal breast were taken as controls and signals from the two sides compared. In 23 patients signals from the normal breast could not be recorded and therefore results of the remaining 82 patients are reported. These included 39 patients with carcinoma, 20 with fibroadenoma, 12 with cyclical nodularity and 11 with cysts. Malignant lumps exhibited significantly higher peak systolic (S) and minimum diastolic frequencies (D) in comparison to the control breast. Fibroadenoma also had a higher S and D than those of the opposite normal breast. Signals over cysts and cyclical nodularity showed no significant difference from the recordings over the control side. Despite significantly higher systolic and diastolic frequencies in the cancer group in comparison to benign lumps and normal breast, considerable overlap in the values was seen between cancer and other groups. Therefore the patterns on 10 MHz Doppler sonography are not sufficiently specific to discriminate benign from malignant breast lumps.

Keywords: Breast disease, diagnosis, Doppler ultrasound

Various diagnostic aids have been employed to help differentiate between benign and malignant breast lumps. Currently mammography is the most commonly used test with a high diagnostic accuracy and high sensitivity. However, recently Smallwood *et al.*[1] found B mode ultrasound scanning of the breast to be highly sensitive (93 per cent) and specific (93 per cent) in a large series of 1000 women presenting with symptomatic breast disease. Mammography in this group was shown to be less sensitive (82 per cent) and less specific (89 per cent).

Since cancers usually show local hypervascularity, assessment of blood flow by Doppler ultrasound might be expected to have discriminatory value in diagnosis of breast lumps. Burns *et al.* in 1982[2] described the use of Doppler ultrasound flowmetry in the detection of blood flow over breat lumps. They were able to distinguish malignant from benign masses by specific blood flow signals.

In the present paper we have evaluated the role of Doppler ultrasound in the diagnosis of breast lumps in a group of 82 patients, using blood flow signals from the corresponding site in the opposite breast as a control.

Patients and methods

One hundred and five patients presenting with discrete breast lumps at the Cardiff Breast Clinic were studied The final diagnoses in these patients were: carcinoma (55), fibroadenoma (20), cysts (12) and discrete lumps which subsequently appeared to be part of a more general nodularity (18) All patients except those with cysts, which were treated by aspiration alone, had either histological or cytological support for the diagnosis

Equipment

Patients were examined by a continuous wave (CW) 10 MHz Doppler ultrasound flowmeter. A Parks 0 5 cm diameter pencil probe (Parks Inc., USA) was used to record the flow signals The Doppler frequency shift signals were recorded on an audio cassette recorder (Akai Ltd, Japan) and waveform spectrum analysis of the signals was performed on the Angioscan II (Unigon Inc., USA) The Angioscan carries out fast Fourier transform analysis of the spectrum. The Doppler flowmeter was assembled at the Department of Bioengineering, University of Wales College of Medicine, Cardiff, UK

Technique

The examination was carried out after 5 min of rest with the patient lying in the supine position. The procedure was explained to the patients and verbal consent obtained. All the cases were examined by a single person, a surgeon who has worked for 2 years full time on Doppler flow studies. The ultrasound probe was applied over and around the breast lump with the ultrasound coupling gel. The angle of the probe was adjusted to get maximum systolic peak on the Angioscan screen These signals were then recorded on the tape for 2–3 min per site. On each lump 4–6 sites were examined and the signals of maximal peak were chosen for the analysis A mirror image site on the opposite breast was also examined (1–2 positions) and signals recorded from vessels in the normal breast The Doppler ultrasound examination was performed before any needle biopsy, and histological confirmation was obtained by aspiration cytology, a needle or open biopsy. The cysts were diagnosed and treated by aspiration

Spectrum analysis

The audio tapes with recorded signals were played on a cassette record player and displayed on the Angioscan screen. The signals with highest peak frequency were selected for analysis. The following measurements were made on three consecutive waves and their average taken·

(1) Peak systolic frequency: the highest frequency on the maximum frequency envelope.
(2) Minimum diastolic frequency· the lowest frequency on the maximum frequency envelope during diastole (D).
(3) Mean systolic frequency· the mean frequency corresponding to the systolic peak (M).

It was not possible to obtain the mean systolic frequency with Angioscan for very feeble signals.

Because recordings over the normal breast showed great variation in different patients the difference of the measurements on the two sides was calculated as follows:

Difference in systolic frequency (S dif)
= systolic frequency over the lump –
systolic frequency over the contralateral
normal breast

Difference in diastolic frequency (D dif.)
= diastolic frequency over the lump –
diastolic frequency over the contralateral
normal breast

Table 1 *Peak systolic frequency (Hz)*

		Over lump			Opposite breast			
Group	*n*	Mean	Median	Standard deviation	Mean	Median	Standard deviation	*P* value
Cancer	39	3315	2720	2746	1577	1320	929	$P<0{\cdot}0001$
Cyclical nodularity	12	2043	1640	1232	1347	1160	766	$P=0{\cdot}1$
Cyst	11	1353	1000	638	1342	1080	733	$P=0{\cdot}9$
Fibroadenoma	20	2170	1680	1275	1298	1240	495	$P=0{\cdot}009$

P values by Mann–Whitney *U* test comparing the signals from the lump with those of the normal breast

Table 2 *Minimum diastolic frequency (Hz)*

		Over lump			*Opposite breast*			
Group	*n*	Mean	Median	Standard deviation	Mean	Median	Standard deviation	*P* value
Cancer	39	1168	760	1446	442	360	285	$P<0{\cdot}0001$
Cyclical nodularity	12	597	460	436	377	340	308	$P=0{\cdot}17$
Cyst	11	342	280	256	331	280	283	$P=1$
Fibroadenoma	20	840	680	690	410	400	150	$P=0{\cdot}01$

P values by Mann–Whitney *U* test comparing the signals from the lump with those of the normal breast

Results

All frequency measurements showed great variation in different patients, e.g. peak systolic frequency ranged between 1200 and 18 000 Hz over malignant lumps and between 480 and 5480 Hz over the normal breast. Therefore, measurements over the normal breast were taken as the control for that patient and the recording over the lump compared with that of the opposite normal breast.

In some patients we could not detect any flow signal over the normal breast at the mirror image site, including one patient who had undergone previous mastectomy and one patient with a large cystic mass. Thus recordings over the lump could not be compared with a contralateral normal signal in 23 patients, and these were excluded from analysis. The diagnoses in the remaining 82 patients were: carcinoma (39), fibroadenoma (20), cyclical nodularity (12) and cysts (11).

The mean systolic frequency (M) could not be measured because of feeble signals in 21 patients with carcinoma, 9 patients with cysts, 11 patients with cyclical nodularity and 13 patients with fibroadenoma. Therefore the results of mean systolic frequency are not given.

The results of frequency measurements have been analysed as follows.

Absolute measurements

The systolic and diastolic frequencies recorded over the lump and over the contralateral normal breast are shown in *Tables 1* and *2*. The data are not normally distributed, hence non-parametric statistical tests were applied.

Peak systolic frequency (S) (Table 1). The mean value of S in the cancer group was 3315 Hz over the lump and 1577 Hz over the normal breast. The difference was highly significant (Mann–Whitney *U* test, $P<0{\cdot}0001$). The mean S values of 2043 Hz in the cyclical nodularity group and 1353 Hz in the cyst group were not different statistically from the normal values recorded over the contralateral breast. Patients with fibroadenoma had a significantly higher systolic frequency over the lump (2170 Hz) when compared with the normal of 1298 Hz.

Inter-group comparison. The peak systolic frequency recorded over the malignant lumps was significantly higher than those over cyclical nodularity, cysts and fibroadenoma as follows: S in cancer *versus* S in cyclical nodularity, $P=0{\cdot}007$; S in cancer *versus* S in cysts, $P=0{\cdot}0001$; S in cancer *versus* S in fibroadenoma, $P=0{\cdot}0008$.

Minimum diastolic frequency (D) (Table 2). The minimum diastolic frequency over the lump in the cancer group was significantly higher than over the normal breast ($P<0{\cdot}0001$). The fibroadenoma group had a higher D over the lump in comparison to the control ($P=0{\cdot}01$). Cyclical nodularity and cysts showed no difference of D from their control normal breast.

Inter-group comparison. The minimum diastolic frequency over the lump was significantly higher in the cancer group when compared with D over cyclical nodularity ($P=0{\cdot}02$) and D over cysts ($P=0{\cdot}0001$). However, D over malignant lumps did not differ from that recorded over fibroadenoma ($P=0{\cdot}17$).

Difference of frequencies on two sides

Tables 3 and *4* show the S dif. and D dif. in the four groups of patients. The S dif. in the cancer group was significantly higher than in the cyclical nodularity and cyst groups. The difference in the S dif. between cancer and fibroadenoma was marginal and did not reach a statistical significance. The D dif. of the cancer group was significantly greater than that of the cyst and cyclical nodularity groups. Fibroadenoma patients did not show any difference from cancer patients in their D dif. values.

Thus Doppler ultrasonic examination of the breast lumps revealed high frequency flow signals over the lump in patients with cancer and fibroadenoma. The peak systolic frequency of the flow signals over malignant lumps was significantly higher both than those of the normal breast and than those over the benign lumps. The diastolic frequency in malignant lumps was also raised from the normal and from those over cyclical

Table 3 *Difference in the peak systolic frequency (S dif.)*

Group	Number	Mean	Median	Standard deviation
Cancer	39	1737	1280	2576
Cyclical nodularity	12	697	500	1172
Cyst	11	11	0	593
Fibroadenoma	20	922	580	1263

P values: cancer *versus* cyclical nodularity = 0·009
cancer *versus* cyst = 0·0001
cancer *versus* fibroadenoma = 0·06

Table 4 *Difference in the minimum diastolic frequency (D dif)*

Group	Number	Mean	Median	Standard deviation
Cancer	39	726	400	1323
Cyclical nodularity	12	697	500	1172
Cyst	11	10·9	0	204·8
Fibroadenoma	20	428	320	707

P values: cancer *versus* cyclical nodularity = 0·03
cancer *versus* cyst = 0·0001
cancer *versus* fibroadenoma = 0·01

nodularity and cysts. Fibroadenoma also displayed higher systolic and diastolic frequency signals from the normal control breast. However these fibroadenoma signals are not different from those of malignant lumps as far as diastolic frequency is concerned. The peak systolic frequency of fibroadenoma showed only slightly lower values than those of the cancer group. Although statistical differences can be shown between the groups, there are wide individual variations and some overlap between different groups.

The peak systolic frequency in the cancer group ranged between 1200 and 18 000 Hz. There were 10 cases of cyclical nodularity, 16 cases of fibroadenoma and 5 cases of breast cyst with a peak systolic frequency > 1200 Hz, thus falling in the range of frequency in the malignant lumps. Minimum diastolic frequency in the cancer group ranged between 280 and 8920 Hz. Doppler flow signals from 5 cysts, 9 cyclical nodularity and 20 fibroadenoma patients had a diastolic frequency within the above range of the cancer group. Thus there was a considerable overlap in the values of S and D among different groups.

Discussion

Although B mode ultrasound scanning is a well described form of breast examination, Doppler ultrasound has not been widely employed in the assessment of breast disease. There are a few reports in the literature on this subject.

In a large series of 404 patients with breast lumps (349 benign lumps, 55 malignant lumps) Burns *et al.*[2] found a 10 MHz CW Doppler ultrasound to be useful in identifying 96 per cent of malignant lumps and 84 per cent of benign lumps. This analysis was based on the auditory features of Doppler signals which were interpreted only by ear. These authors carried out spectrum analysis in 18 normal controls and 23 patients with malignant lumps from the above series. In this small number of cases assessed objectively they found a statistically highly significant increase in maximum systolic, mean and minimum diastolic frequencies recorded over cancer in comparison to those of the normal breast.

In another small series Wells *et al.*[3], using a 10 MHz CW Doppler flowmeter, studied nine patients (six benign lumps, three malignant lumps). The result was interpreted by ear. They found the Doppler ultrasound 100 per cent accurate in predicting the diagnosis. Bamber *et al.*[4] studied the blood flow in 24 patients with breast cancer using a 10 MHz CW Doppler flowmeter. They reported a significantly higher mean frequency over all the malignant lumps in comparison to the opposite normal breast. Gros *et al.*[5] using a pulsed 8 MHz flowmeter in 24 patients with malignant breast lumps found the test to have a diagnostic accuracy of 67 per cent. They used only subjective auditory analysis of signals. Two other reports by Lypacewicz *et al.*[6] and White and Cledgett[7] using 5 MHz and 4·5 MHz Doppler flowmeters respectively are not comparable to our study as a low frequency flowmeter is much less sensitive for superficial vessels.

This first large study of Doppler sonography on breast lumps reporting the result on the basis of objective spectrum analysis has not confirmed the diagnostic specificity recorded in some of these earlier studies.

Although statistical analysis of data taking the whole group shows significant differences in maximum systolic and minimum diastolic frequencies in cancer patients in comparison to other groups, the range of values is very wide. There is an overlap of frequencies between different groups. Therefore we feel that a 10 MHz CW Doppler flowmeter is not useful in the diagnosis of breast lumps. However, ultrasound technology is changing rapidly. Development of more advanced probes with high sensitivity and resolution, perhaps in conjunction with real time imaging and use of more sophisticated forms of signal analysis, may help in the detection of subtle differences in the blood flow pattern of breast lumps of different nature and may improve the present diagnostic accuracy.

Acknowledgements

The authors are grateful to Miss Mary Ryan, Mrs Jane Hopkins and Mrs Enid Davies for the preparation of the script This work was supported by the Cancer Research Campaign

References

1. Smallwood JA, Guyer P, Dewbury K *et al* The accuracy of ultrasound in the diagnosis of breast disease *Ann R Coll Surg Engl* 1986, **68** 19–22
2. Burns PN, Halliwell M, Wells PNT, Webb AJ. Ultrasonic Doppler studies of the breast. *Ultrasound Med Biol* 1982, **8**. 127–43.
3. Wells PNT, Halliwell M, Skidmore R, Webb AJ, Woodcock JP Tumour detection by ultrasonic Doppler blood flow signals *Ultrasonics* 1977; **15**. 231–2.
4. Bamber JC, Sambrook M, Minasian H, Hill CR. Doppler study of blood flow in breast cancer. In: Jellins J, Kobayashi T, eds *Ultrasonic Examinations of the Breast* Chichester: Wiley, 1983 371–8.
5. Gros CM, Dale G, Gairand B. Breast echography· criteria of malignancy and results. In: Kurjak A, ed *Recent Advances in Ultrasound Diagnosis*. Amsterdam: Excerpta Medica, 1978 292–8
6. Lypacewicz G, Powalowski T, Lukawska K. Ultrasonic examination of breast tumours with Doppler method In. Filipczynski L, Zieniuk JK, eds *Proc 2nd Congress of the Federation of Acoustical Societies of Europe*, Vol II Warsaw Polish Academy of Sciences, 1978 153–6
7. White DN, Cledgett PR Breast carcinoma detection by ultrasonic Doppler signals. *Ultrasound Med Biol* 1978, 4: 329–35

Paper accepted 22 May 1988

Br. J. Surg. 1988, Vol. 75, September,
854–856

Effect of intraperitoneal saline irrigation at different temperatures on adhesion formation

A. M. Kappas,
M. Fatouros,
K. Papadimitriou*,
V. Katsouyannopoulos†
and D. Cassioumis

Department of Surgery and
**Department of Pathology,*
University of Ioannina, Hatzikosta
General Hospital, Ioannina, Greece
and †University of Ioannina,
Ioannina, Greece
Correspondence to:
Dr A. M. Kappas, 4 Papajoglou
Street, 454 44 Ioannina, Greece

This study was designed to examine the influence of saline irrigation at different temperatures on adhesion/formation in the rat. Saline irrigation through a laparotomy incision was performed at the following temperatures: 30°C, 34°C, 37°C, 40°C, 45°C, 50°C, 55°C, and 60°C. The control group (G_c, n = 20) underwent laparotomy without irrigation. Adhesions were found in: 5/20 animals of the G_c (all slight); 6/20 of the 30°C group (all slight); 6/20 of the 34°C group (all slight); 6/20 of the 37°C group (all slight); 12/20 of the 40°C group (all slight); 12/20 of the 45°C group (11 slight, 1 moderate); 14/20 of the 50°C group (12 slight, 2 moderate); 18/19 of the 55°C group (2 slight, 6 moderate, 10 marked); and 18/18 of the 60°C group (1 moderate, 8 marked, 9 massive). These results indicate that saline irrigation below body temperature does not prevent adhesions whereas warmed saline encourages adhesion formation in the rat.

Keywords: Peritoneal adhesions, intraperitoneal saline irrigation

Intra-operative irrigation of the peritoneal cavity with isotonic saline solution (0·9 per cent) is often used empirically to reduce the bacterial inoculum following contaminated operations as well as a means of removing blood, bile and other adjuvants of bacterial infection[1–4]. The volume of saline used varies from 1 to 10 litres depending on the severity of peritonitis and degree of contamination[1,2]. The temperature of saline used is often variable and may range from 30°C to 50°C. Although warm saline is often recommended accurate temperature control is rarely observed[5–10]. Few experimental or clinical studies have correlated saline irrigation with adhesion formation apart from one experimental observation indicating that saline irrigation, at normal temperature, combined with intra-abdominal manipulations caused more adhesions than no irrigation at all[11].

The aim of the present study was to assess the effect of peroperative intraperitoneal saline irrigation at different temperatures on adhesion formation in the rat.

Materials and methods

One hundred and eighty syngeneic Wistar rats weighing 230–300 g were randomly allocated into nine groups (eight experimental and one control) with twenty animals each. The operations were performed under general anaesthesia using ether, ketamine, diazepam and oxygen. After thoroughly cleansing the abdomen and having ensured that all powder had been removed from gloves, the abdomen was opened through a 4·5–5 cm midline incision Laparotomy was followed in the control group (G_c) by immediate closure with continuous polyglycolic acid sutures (3/0) in two layers while in the experimental groups laparotomy was followed by intraperitoneal saline irrigation using normal saline (0 9 per cent) for 5 min. The temperature of the saline throughout the irrigation was. 30°C (group G_{30}); 34°C (group G_{34}), 37°C (group G_{37}); 40°C (group G_{40}); 45°C (group G_{45}); 50°C (group G_{50}); 55°C (group G_{55}); and 60°C (group G_{60}). The volume of the irrigated saline in each animal was standardized at 40 ml After completion of the irrigation the abdomen was closed using continuous polyglycolic acid sutures (3/0) in two layers as in the controls (G_c)

All animals were killed in groups of five using ether at 1, 2, 4 and 12 weeks after laparotomy. Three animals (1 of the G_{55} and 2 of the G_{60}) died from peritonitis due to intestinal perforation associated with adhesion formation.

Macroscopic assessment of adhesions was graded [11–13] by an independent observer into the following groups· 0, no adhesions; 1, slight adhesions (1–3 bands or adhesions to the laparotomy scar with a length of attachment less than 1/2 of the scar length), 2, moderate adhesions (more than 3 bands or adhesions to an intestinal loop or adhesions with a length of attachment 1/2–2/3 of the scar length), 3, marked adhesions (adhesions to more than 1 intestinal loop or adhesions with a length of attachment more than 2/3 of the scar length), and 4, massive adhesions (involving many organs).

Adhesions were photographed and the involved organs were excised and stored in 10 per cent formalin. Specimens were processed for paraffin sections and evaluated by an independent pathologist.

Statistical analysis of our data was carried out using the Biomedical programs package (University of California Press, Berkeley, Los Angeles, London 1981). Correlation between severity of adhesions and temperature was determined using Kendall's τ correlation coefficient after score transformation The χ^2 test (with or without Yates' correction) was applied where appropriate

Results

Macroscopic estimation of adhesions

Macroscopic assessment of adhesions is summarized in *Table 1.* Statistically significant differences for the presence of adhesions between the experimental groups and the controls (G_c) were identified in groups G_{40}–G_{60}. Comparison between G_{37} and the other experimental groups revealed significant differences in groups: G_{50}–G_{60} (*Table 1*). Kendall's correlation coefficient, after score transformation, showed that there was a positive correlation between the temperature of saline and the total score for the severity of adhesions of each group ($\tau = 0{\cdot}95$, $P = 0{\cdot}002$).

The correlation between the participation of each organ in adhesions and the temperature of saline is analysed in *Table 2.* Statistically significant correlations ($P \leqslant 0{\cdot}05$) were found in the incidence of adhesions to the following sites: laparotomy scar, small intestine, large intestine, omentum, parietal peritoneum and the internal genitalia. Analysis of the participation of the small intestine to adhesion formation showed a highly significant difference between G_{55} and G_{60} *versus* controls ($\chi^2 = 15{\cdot}401$, d.f. = 1, $P = 0{\cdot}0001$, $\chi^2 = 30{\cdot}467$, d.f. = 1, $P < 0{\cdot}0001$)

This paper was presented in part to the Peritoneum and Peritoneal Access Congress, June 1987, Lund-Sweden

Table 1 *Number of animals with adhesions and grading (severity) of adhesions in control and experimental groups*

Experimental group	No adhesions n	Adhesions n	Adhesions' grading* (n) 1	2	3	4	Total animals in each group
G_c	15	5	5				20
G_{30}	14	6	6				20
G_{34}	14	6	6				20
G_{37}	14	6	6				20
G_{40}	8	12**	12				20
G_{45}	8	12**	11	1			20
G_{50}	6	14**†	12	2			20
G_{55}	1	18**†	2	6	10		19 (1)
G_{60}		18**†		1	8	9	18 (2)
Total	80	97	60	10	18	9	177

G_c, control group; G_{30}, saline at 30°C, G_{34}, saline at 34°C; G_{37}, saline at 37°C; G_{40}, saline at 40°C; G_{45}, saline at 45°C; G_{50}, saline at 50°C; G_{55}, saline at 55°C; G_{60}, saline at 60°C; *1, slight; 2, moderate; 3, marked; 4, massive, **$P<0·05$ compared with G_c; †$P<0·05$ compared with G_{37}; values in parentheses are deaths due to peritonitis

Table 2 *Correlation between participation of each organ in adhesions and the temperature of saline*

Organs	Adhesions in control and experimental groups G_c	G_{30}	G_{34}	G_{37}	G_{40}	G_{45}	G_{50}	G_{55}	G_{60}	Kendall's correlation coefficient τ	P
Laparotomy scar	2	4	4	6	8	9	7	15	17	0·83	0·01*
Small intestine	0	0	0	0	0	0	1	12	17	0·80	0·01*
Large intestine	0	0	0	0	0	0	0	4	12	0·68	0·05*
Omentum	3	3	4	3	8	7	8	17	15	0·74	0·01*
Stomach	0	0	0	0	0	1	1	0	5	0·59	0·1
Spleen	0	0	0	2	3	0	3	1	3	0·48	0·1
Liver	2	2	2	0	5	5	2	4	4	0·27	0·4
Parietal peritoneum	0	0	0	0	0	0	0	4	6	0·68	0·05*
Internal genitalia and folds	3	3	2	5	10	6	9	16	17	0·78	0·01*

G_c, control group; G_{30}, saline at 30°C; C_{34}, saline at 34°C; G_{37}, saline at 37°C; G_{40}, saline at 40°C; G_{45}, saline at 45°C; G_{50}, saline at 50°C; G_{55}, saline at 55°C; G_{60}, saline at 60°C; *$P \leqslant 0·05$

Table 3 *Presence of adhesions in each group according to the survival time of animals*

Experimental group	Animals with adhesions (total animals in each group) 1 week	2 weeks	4 weeks	12 weeks
G_c	3 (5)	1 (5)	1 (5)	0 (5)
G_{30}	2 (5)	3 (5)	0 (5)	1 (5)
G_{34}	3 (5)	2 (5)	1 (5)	0 (5)
G_{37}	3 (5)	1 (5)	2 (5)	0 (5)
G_{40}	5 (5)	4 (5)	3 (5)	0 (5)
G_{45}	2 (5)	4 (5)	3 (5)	3 (5)
G_{50}	3 (5)	4 (5)	3 (5)	4 (5)
G_{55}	5 (5)	5 (5)	4 (5)	4 (4)*
G_{60}	5 (5)	5 (5)	4 (4)*	4 (4)*

G_c, control group; G_{30}, saline at 30°C, G_{34}, saline at 34°C; G_{37}, saline at 37°C; G_{40}, saline at 40°C; G_{45}, saline at 45°C; G_{50}, saline at 50°C; G_{55}, saline at 55°C; G_{60}, saline at 60°C; *deaths

respectively while the difference between G_{55} and G_{60} was not significant ($\chi^2=2·4$, d.f.$=1$, $P=0·12$).

In *Table 3* the number of animals in each group with adhesions is recorded according to the surviving time. There was no difference between the controls G_c and groups G_{30}–G_{37}. In G_{40} there were more adhesions between weeks 1 and 4 than in the groups having irrigation at lower temperatures but the difference was not statistically significant. Groups G_{45}–G_{60} did not follow the same pattern as controls, and there was a significantly higher incidence of adhesions between weeks 1 and 12 in the animals of groups G_{45}–G_{60} compared with G_{30}–G_{40} ($\chi^2=5·838$, d.f.$=1$, $P=0·015$).

Discussion

Ever since Price[14,15] introduced peritoneal irrigation for treatment of peritonitis, its usefulness has been questioned. Maingot[16] suggests that peritoneal irrigation is never justified even in the presence of gross faecal contamination. Conversely Artz *et al.*[1] and Hudspeth[2] suggest that this procedure has reduced morbidity.

In the present study, using saline at different temperatures, we tried to assess the influence of temperature on adhesion formation. Adhesion formation increased when the temperature of saline exceeded 37°C. The organs most frequently involved in adhesion formation in this experimental model were the laparotomy scar followed by the internal genitalia with their folds, the omentum and the small intestine. However, the number of adhesions in laparotomy scar and small intestine had the highest correlation with increase in temperature (τ values 0·83 and 0·80 respectively). The participation of the small intestine in adhesion formation became statistically significant in groups G_{55} and G_{60}. This suggests that the irrigation solution should certainly be cooler than 50°C. Furthermore there was a tendency for persistence of adhesions after the first week in groups G_{45}–G_{60}. Conversely in groups G_{30}–G_{40} a waning presence of adhesion was noticed between weeks 1 and 12. The above observation might be explained as a possibility of spontaneous resolution of some slight adhesions during this period. Spontaneous resolution of adhesions has already been mentioned in the human situation[17].

The formation of small arteries, that was observed in the adhesions in our study, confirms the view of Jagelman and Ellis[17,18] that adhesions are useful vascular grafts preventing gangrene and perforation of the luminal organs.

Three animals died from intestinal perforation combined with severe adhesion formation. This injury may be associated with intestinal ischaemia[19–21] and our study suggests that a mucosal lesion may develop in association with adhesions when the irrigating fluid temperature exceeded 50°C, particularly as the small intestine was usually involved in the adhesion process.

While it is dangerous to extrapolate from animal models to man, these data do suggest that potentially dangerous adhesions are encouraged when the temperature of saline irrigating fluid exceeds 37°C.

Acknowledgements

We wish to thank Professor M. R. B. Keighley for his advice in the design and analysis of this study.

References

1 Artz CP, Barnett WO, Grogan JB Further studies concerning the pathogenesis and treatment of peritonitis. *Ann Surg* 1962; **155**: 756–67

2. Hudspeth AS. Radical surgical debridement in the treatment of advanced generalized peritonitis. *Arch Surg* 1975; **110**: 1233–6

3. Ambrose NS, Donovan IA, Derges S, Minervini S, Harding LK The efficacy of peritoneal lavage at elective abdominal operations. *Br J Surg* 1982, **69**: 143–4.

4. Nystrom PO, Johansson L, Lennquist S. Intra-operative saline irrigation of the peritoneal cavity in experimental post-traumatic peritonitis. *Acta Chir Scand* 1983; **149**: 509–15.

5. Quénu J, Loygue J, Perrotin J, Dubost C, Moreaux J, eds Laparotomies pour péritonites aigues diffuses. *Operations sur les Parois de l'Abdomen et sur le Tube Digestif.* Paris: Masson 1967: 1153–81.

6. Dunphy JE Peritoneal cavity. In: Way LW, ed. *Current Surgical Diagnosis and Treatment*. California: Lange Medical Publications 1983: 422–36

7. Block GE, Guiliano AE Operations for inflammatory bowel disease. *Surg Clin North Am* 1977; **57**: 1235–51.

8. Freeark RJ. Blunt torso trauma *Surg Clin North Am* 1977; **57**: 1317–33.

9. Hau T, Van Hook EJ, Simmons RL, Najarian JS. Prognostic factors of peritoneal infections in transplant patients. *Surgery* 1978; **84**: 403–16.

10. Hau T, Ahrenholz DH, Simmons RL. Secondary bacterial peritonitis: The biologic basis of treatment. *Curr Probl Surg* 1979; **26**: 34–43.

11. Phillips RKS, Dudley HAF. The effect of tetracycline lavage and trauma on visceral and parietal peritoneal ultrastructure and adhesion formation. *Br J Surg* 1984, **71**: 537–9.

12. Goldberg EP, Sheets JW, Habal MB. Peritoneal adhesions. *Arch Surg* 1980, **115**: 776–80.

13. Lindenberg S, Moesgaard F, Vangsted P, Nielsen ML. Peritoneal dialysis reduces intraperitoneal adhesion formation. *Eur Surg Res* 1982; **14**: 274–8.

14 Price J. Surgical intervention in cases of general peritonitis *Proceedings of the Philadelphia County Medical Society* 1905; **26**: 192.

15. Price J. Surgical intervention in cases of general peritonitis from typhoid fever and acute gonococcal infection. *Am Med* 1905; **9**: 769.

16. Maingot R. Acute peritonitis. In: Maingot R, ed *Abdominal Operations*, 6th edn. New York: Appleton-Century-Crofts, 1974: **2**: 1416.

17. Jagelman DG, Ellis H. Starch and intraperitoneal adhesion formation. *Br J Surg* 1973; **60**: 111–14.

18 Ellis H. The causes and prevention of intestinal adhesions. *Br J Surg* 1982, **69**: 241–3.

19. Haglund U, Lundgren O. Intestinal ischemia and shock factors *Fed Proc* 1978; **37**: 2729–33.

20. Parks DA, Bulkley GB, Granger DN, Hamilton SR, McCord JM. Ischemic injury in the cat small intestine: role of superoxide radicals. *Gastroenterology* 1982; **82**: 9–15.

21. Parks DA, Bulkley GB, Granger DN Role of oxygen-derived free radicals in digestive tract diseases. *Surgery* 1983, **94**: 415–22.

Paper accepted 8 May 1988

Br. J. Surg. 1988, Vol. 75, September, 857–861

Ten-year computerized audit of infection after abdominal surgery

Z. H. Krukowski and N. A. Matheson

Department of Surgery, University of Aberdeen, Aberdeen, UK
Correspondence to:
Mr Z. H. Krukowski, Department of Surgery, Medical School,
Aberdeen Royal Infirmary,
Foresterhill, Aberdeen AB9 2ZD,
UK

A prospective audit of the frequency of infective complications after all abdominal operations was carried out between January 1977 and December 1986. A total of 3100 abdominal procedures (2041 elective; 1059 emergency) were performed in 3056 patients. There were 50 (1·6 per cent) in-hospital and 66 (2·1 per cent) late wound infections (overall 3·7 per cent). Fifty-four (1·8 per cent) patients developed postoperative intraperitoneal sepsis. Ninety-eight patients died (overall mortality 3·2 per cent) and intraperitoneal sepsis was a related factor in twelve (0·4 per cent). Wound infection, peritoneal sepsis and mortality were related to the degree of operative contamination and to reoperation. The results support the traditional, although sometimes inadequately stressed, teaching that technique is an important factor in preventing infection. Infection is also reduced by peroperative antibiotic lavage. The limited value and the potential difficulties of the unstructured introduction of computerized audit should be recognized.

Keywords: Postoperative wound infection, computerized audit

Sepsis remains the most important potentially avoidable source of morbidity and mortality in abdominal surgery. Despite a growing consensus on the indications, spectrum of activity and route of administration of prophylactic antibiotics, the frequency of sepsis-related mortality and morbidity is remarkably variable. The differing experience of some centres in the United Kingdom compared with those in the United States with similar antibiotic regimens has recently been the subject of unfavourable comment[1]. However, the accurate documentation of postoperative sepsis is onerous and rarely performed outside small clinical trials. We present the results and an analysis of the influence of a prospective computerized study of 10 years' duration on the outcome of 3100 consecutive abdominal operations. A consistent policy for the prophylaxis and treatment of abdominal infection was modified only as a result of analysis of the first 5-year period[2].

Patients and methods

Definitions

Wound infection. This refers to the discharge of pus or of a serous or sanguinous discharge that grew a pathogenic organism. All patients who at follow-up reported a discharge from their wound were considered to have had an infected wound.

Intraperitoneal sepsis. This was recorded when pus was drained, aspirated, or discharged from the peritoneal cavity or if there was radiological, ultrasonic, or necropsy evidence of an intraperitoneal collection.

Operative contamination. This was classified as follows, based on the American NRC criteria[3]. *clean*—no infection encountered, no hollow abdominal viscus opened; *clean/contaminated*—hollow abdominal viscus opened with minimal spillage of contents; *contaminated*—inflammation without pus formation, viscus opened with gross spillage of contents; *dirty*—pus encountered or perforated viscus found.

Data collection and analysis

From January 1977 to December 1986 all patients undergoing an abdominal operation under the care of one consultant were included. Information was recorded on standard forms on completion of the operation, on discharge from or death in hospital and at follow-up 4–6 weeks after discharge. In 84 (2·7 per cent) patients unable or unwilling to attend, the information was obtained from their general practitioner. Patients with advanced malignant disease (23), 8 of whom died within 4 weeks of discharge, were not asked to attend for review, 10 patients from outside the region could not attend; 44 were either not asked to attend for various reasons (often advanced age and debility), or failed to attend despite repeated requests. Follow-up was 97·5 per cent complete.

The information was analysed using a microcomputer connected to a Honeywell 66/80 mainframe computer using SPSSX

Surgical management

A standard surgical policy was followed throughout The skin was shaved after induction of anaesthesia and prepared with 0·5 per cent chlorhexidine in 70 per cent alcohol. All laparotomies were performed through a vertical midline incision. A midline incision was also used if a diagnosis of perforated appendicitis with generalized peritonitis had been made. Wound towels were used routinely, except for groin hernia repair, and were supplemented with a plastic ring drape when a hollow viscus was opened, except in uncomplicated cholecystectomy Incisions were closed with a continuous mass suture (polypropylene or, since 1983, polydioxanone) without subcutaneous sutures and primary skin closure was routine with one exception 'Clean' transverse skin crease incisions for groin hernia repair were closed with subcuticular polyglycolic acid.

Bowel preparation for elective left-sided colonic resection was by whole gut irrigation[4] with 20 litres electrolyte solution containing 20 g neomycin and 1·6 g metronidazole. For right-sided colonic resections three bowel washouts and oral metronidazole 600 mg were given In a few selected patients, 'on table' irrigation[5] was used to prepare the bowel for primary anastomosis after emergency resection of the left colon.

Intestinal anastomoses were made with an appositional technique using a single layer of interrupted serosubmucosal braided polyamide[6]. Drains were very largely avoided and never used in peritonitis or as a safeguard against anastomotic leakage, but small-bore suction drains were occasionally used for 48 h after pancreatic or biliary surgery and after mobilization of the rectum when continued oozing was expected

In emergency surgery for peritonitis, resection of the source of peritoneal contamination was a rule except in uncomplicated perforated duodenal ulcer and in two patients with acute diverticulitis without obvious perforation

Antibiotic policy

Throughout the 10 years, antibiotic policy in patients with any degree of contamination was based on peroperative lavage of the peritoneal cavity and abdominal wound with tetracycline solution (1 g/litre 0·9 per cent saline) together with a single intravenous peroperative dose of 500 mg tetracycline[7]. The volume used for lavage varied with the degree of contamination between 500 ml and several litres.

Before 1983, additional therapeutic antibiotics for peritoneal infection

Table 1 *The relationship of wound infection to operative contamination*

	Elective			Emergency			Overall		
		Infected			Infected			Infected	
	Total	(No.)	(%)	Total	(No.)	(%)	Total	(No.)	(%)
Clean	755	34	4·5	139	7	5·0	894	41	4·6
Clean/contaminated	872	18	2·1	327	7	2·1	1199	25	2·1
Contaminated	362	8	2·2	244	10	4·1	606	18	3·0
Dirty	52	3	5·8	349	29	8·3	401	32	8·0
Overall	2041	63	3·1	1059	53	5·0	3100	116	3·7

Table 2 *Incidence of wound infections by operative procedure**

	Elective			Emergency			Overall		
		Infected			Infected			Infected	
	Total	(No.)	(%)	Total	(No.)	(%)	Total	(No.)	(%)
Upper gut	451	19	4·2	166	6	3·6	617	25	4·1
Highly selective vagotomy	192	11	5·7	12	—	—	204	11	5·4
Vagotomy and drainage	124	4	3·2	83	2	2·4	207	6	2·9
Gastrectomy	70	2	2·9	38	2	5·3	108	4	3·7
Small bowel	59	2	3·4	83	9	10·8	142	11	7·7
Resection and anastomosis	37	2	5·4	46	2	4·3	83	4	4·8
Appendix	38	1	2·6	456	17	3·7	494	18	3·6
Perforated	—	—	—	117	9	7·7	—	—	—
Colorectal	328	9	2·7	148	13	8·8	476	22	4·6
Ileo-colic anastomosis	67	2	3·0	47	5	10·6	114	7	6·1
Colo-colic/rectal anastomosis	185	4	2·2	27	2	7·4	212	6	2·8
Hartmann/total colectomy	13	—	—	51	4	7·8	64	4	6·3
APER/proctocolectomy	31	2	6·5	2	1	50·0	33	3	9·1
Loop colostomy	4	—	—	5	1	20·0	9	1	11·1
Pancreaticobiliary	694	14	2·0	76	2	2·6	770	16	2·1
All cholecystectomy	580	9	1·6	56	1	1·8	636	10	1·6
All exploration of CBD	177	7	4·0	13	—	—	190	7	3·7
Other	589	21	3·6	200	11	5·5	789	32	4·1
Inguinal hernia	344	14	4·1	19	2	10·5	363	16	4·4
Other hernia	96	6	6·3	34	3	8·8	130	9	6·9

* Column totals exceed 3100 and 116 wound infections because some patients had two or more operative procedures (e.g. highly selective vagotomy and cholecystectomy) and therefore feature more than once. APER, abdominoperineal excision of rectum, CBD, common bile duct

extant at the time of operation were given on an individual basis either as IV tetracycline or as a combination of antibiotics for 3–7 days.

After 1983 all patients with peritonitis of small bowel, appendicular or colonic origin were given supplementary ampicillin, gentamicin and metronidazole intravenously for 3 days. Patients with gangrenous but non-perforated appendicitis received a single supplementary peroperative dose of 500 mg metronidazole. In addition, patients undergoing a 'clean' laparotomy lasting more than 1 h received a single peroperative intravenous dose of 1 g cloxacillin instead of intravenous and topical tetracycline. A chlorhexidine shower was also introduced as a routine before elective operations.

Results

During the 10 years there were 3100 operations on 3056 patients. The distribution of wound infection according to the degree of operative contamination and type of operation is shown in *Table 1*. There was no significant difference in the annual incidence of wound infection over the 10 years and no evidence of a diminishing frequency of infection during the audit. Of the 116 wound infections, 66 (56·9 per cent) presented late after the patient had left hospital. There were 32 (8·0 per cent) wound infections in 401 'dirty' procedures but only 22 (5·5 per cent) presented in hospital, the remainder being detected or reported at follow-up.

Wound infection was significantly more common after all emergency operations (5·0 per cent emergency *versus* 3·1 per cent elective; χ^2 6·60; $P<0·02$) (*Table 1*) particularly after colonic and small bowel procedures (*Table 2*).

The effect of the change in antibiotic policy on peritonitis of distal intestinal origin is shown in *Table 3*. The reduction was not significant.

There were a surprising number of wound infections (41; 4·6 per cent) in 'clean' cases throughout the 10 years although this was largely attributable to the 33 minor episodes recorded at follow-up. The infected 'clean' wounds comprised 19 inguinal hernia and 4 midline abdominal hernia repairs, 8 highly selective vagotomies, 3 laparotomies for adhesive small bowel obstruction and 7 miscellaneous laparotomies. Bacteriological confirmation was available in only 14 of the 33 'late' infections. There was a statistically non-significant reduction in the frequency of wound infection in elective 'clean' cases after 1983 (pre-1983, 18/341 (5·3 per cent) *versus* post-1983, 16/414 (3·9 per cent)) but an increase in emergency 'clean' cases (pre-1983, 1/83 (1·2 per cent) *versus* post-1983, 6/56 (10·7 per cent); $P<0·05$, Fisher's exact test). There was a reduction in wound sepsis after highly selective vagotomy with only 1 (1·2 per cent) wound infection in 83 cases after 1983 compared with 10 (8·3 per cent) in 120 before the change in policy ($P<0·05$, Fisher's exact test).

Staphylococci were cultured from 88·9 per cent of infected 'clean' wounds, compared with 34·8 per cent of all contaminated wounds. The frequency of proven staphylococcal wound sepsis in 'clean' cases was 16 (1·8 per cent) in 894 compared with 15

Table 3 *Wound sepsis in patients with peritonitis of small bowel, appendicular or colonic origin in relation to a change in antibiotic policy. None of the differences was significant*

	No. of operations	In-hospital wound infection (No.)	In-hospital wound infection (%)	Late wound infection (No.)	Late wound infection (%)	Total wound infections (No.)	Total wound infections (%)
Pre 1983	139	11	7·9	5	3·6	16	11·5
Post 1983	106	6	5·7	4	3·8	10	9·4
Overall	245	17	6·9	9	3·7	26	10·6

Table 4 *The relationship of intraperitoneal sepsis to operative contamination*

	Elective			Emergency			Overall		
	Total	(No.)	(%)	Total	(No.)	(%)	Total	(No.)	(%)
Clean	755	1	0·1	139	—	—	894	1	0·1
Clean/contaminated	872	12	1·4	327	3	0·9	1199	15	1·3
Contaminated	362	8	2·2	244	4	1·6	606	12	2·0
Dirty	52	5	9·6	349	21	6·0	401	26	6·5
Overall	2041	26	1·3	1059	28	2·6	3100	54	1·7

$\chi^2 > 30{\cdot}00$, d.f. = 3; $P < 0{\cdot}001$ for all columns

(0·7 per cent) in the remaining 2206 cases. This difference was significant (χ^2 6·88; d.f. = 1; $P < 0{\cdot}01$).

The frequency of postoperative intraperitoneal sepsis in relation to operative contamination is shown in *Table 4*. In 22 patients anastomotic or suture-line leakage was confirmed radiologically or at reoperation. The frequency of postoperative sepsis increased with the degree of operative contamination in both elective and emergency cases ($\chi^2 > 30$; d.f. = 3; $P < 0{\cdot}001$).

Of the 3056 patients, 98 (3·2 per cent) died within 30 days or during the surgical admission (whichever was longer). Peritoneal sepsis was a mortality-related factor in 12 (0·4 per cent) patients: 6 of them presented with sepsis of colonic origin and 3 were aged (> 75 years); 4 had an anastomotic leak and 2 had postoperative pancreatitis.

In the 1059 emergency procedures there were 967 first, 71 second, 14 third, 4 fourth and 3 fifth separate operations. The morbidity and mortality increased if a second or subsequent operation was required for any reason or at any time interval (*Figure 1*).

Discussion

This unselected consecutive series of abdominal operations was carried out in one general surgical service which included an emergency commitment to take all general surgical emergency admissions from a population of 500 000 every eighth day. Although this series was based in the major teaching hospital in North-East Scotland, the workload may be considered representative of a typical district general hospital. The patients were not entered into any comparative studies of antibiotic prophylaxis and the data were collected prospectively. The criteria for diagnosis of wound infection remained constant throughout the 10 years and the frequency of wound infection may be an overestimate because bacteriological confirmation from a wound discharge was not a prerequisite.

The operative strategy remained essentially unchanged throughout the period under review although there was a trend towards non-operative management of perforated acute diverticulitis[8]. The management of peritoneal and parietal contamination was as previously described by us and the antibiotic policy was based on peroperative lavage of the wound and peritoneum with tetracycline (1 mg/ml) in 0·9 per cent saline. As a consequence of analysis of the first 5 years of this study[2], the use of supplementary antibiotics in established peritoneal sepsis of distal intestinal origin was changed in 1983 from an individual basis to a policy of triple antibiotics (metronidazole, gentamicin and ampicillin for 3 days). In addition, patients undergoing highly selective vagotomy or a 'clean' laparotomy lasting more than 1 h received a single intravenous dose of cloxacillin. These changes both led to a small but statistically non-significant decrease in the overall frequency of wound sepsis in these groups The frequency of wound sepsis after highly

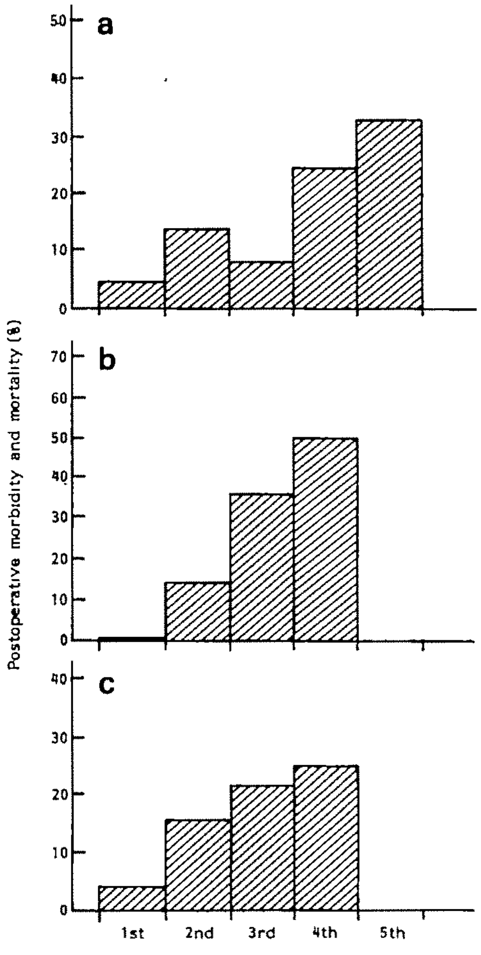


Figure 1 *Increasing frequency of postoperative morbidity and mortality with multiple operations* **a** *Wound infection*, **b** *intraperitoneal sepsis*, **c** *mortality*

selective vagotomy however showed a significant and worthwhile improvement.

Wound infection in hospital was very uncommon, especially after elective abdominal surgery, and when present was always minor. The importance of adequate follow-up in the critical assessment of the frequency of wound infection is reinforced: the majority (56·9 per cent) of wound infections were detected after discharge from hospital. However, all of these infections were trivial and of very little clinical importance. The difficulties of securing follow-up in 97·5 per cent of the patients were substantial and involved much more effort and correspondence than the clinical condition would otherwise have warranted.

In 'clean' surgery our infection rate has been disappointingly high (4·6 per cent) although it should be stressed that the in-hospital rate was below 1 per cent and that bacteriological confirmation of wound sepsis was present in only 42 per cent of patients who had a wound discharge after leaving hospital and which, according to our definition, was recorded as a wound infection. In groin hernia repairs the use of continuous subcuticular skin closure with a slowly absorbed suture material may be a factor in the number of late discharges from such wounds compared with vertical incisions closed with interrupted skin suturing. Furthermore, the significantly higher incidence of staphylococcal wound sepsis in this group of patients in whom wound towels and tetracycline lavage was not routine, suggests that these measures may also be relevant.

The frequency of wound infection in 'clean-contaminated' (2·1 per cent), 'contaminated' (3·0 per cent) and 'dirty' (8·0 per cent) operations is lower than in other unselected series, particularly the large study by Cruse and Foord[9] who reported rates of 7·7 per cent, 15·2 per cent and 40·0 per cent respectively, and much lower than has often been reported from the United Kingdom in clinical trials of prophylactic antibiotic regimens. After elective colorectal surgery (*Table 2*) in particular, our experience is more consistent with North American reports[10,11]. Such differences have been attributed to variations in the antibiotic sensitivities of the bacterial population, the nature and complexity of the surgery performed and the accuracy of data collection[12]. Operative technique may also be an important determinant and our consistent use of peroperative antibiotic lavage is likely to be an additional factor in the present results.

The relatively consistent antibiotic policy during the present study permits analysis of a large unselected consecutive group of patients in whom antibiotic prophylaxis and therapy was based on peroperative antibiotic lavage. The results of the study confirm the clinical efficacy of this economical antibiotic practice and support the experimental observation that a single peroperative lavage is as effective as a prolonged course of systemic antibiotics[13]. Although many of the bacteria present in peritoneal contamination are resistant to tetracycline in conventional blood and tissue concentrations, there is no known resistance[14] at the high topical concentrations to which they are exposed at lavage. In addition we have recently shown that, in patients with peritonitis, tetracycline lavage abolishes bacterial growth in the peritoneal cavity[15]. A similar effect was not achieved with saline lavage together with systemic antibiotics.

The only major change in antibiotic usage during 10 years, excepting the minor changes in clean wounds, was the rationalization (and increased use) of therapeutic antibiotics during and after 1983 in patients with peritonitis of distal intestinal origin, an area with apparent potential for improvement. This change resulted in a small (but statistically non-significant) reduction in the frequency of wound sepsis in this category of patient (*Table 3*). The low incidence and generally minor nature of wound sepsis during the 10 years supports our contention that routine delayed or non-closure of the wound in even 'dirty' procedures is unnecessary. Primary healing occurred in 94·6 per cent of all 'dirty' procedures although a further 2·5 per cent reported discharge from the wound after leaving hospital. There may be a place for delayed closure in patients with established sepsis undergoing reoperation, but we are unconvinced.

Postoperative peritoneal sepsis is a more critical consideration than wound infection but is difficult to quantify accurately. Patients with suspected postoperative intraperitoneal sepsis were intensively investigated to establish the diagnosis and, wherever possible, the cause. We have discontinued routine water-soluble contrast studies of left-sided colonic anastomoses since 1975 but, when there was clinical suspicion of anastomotic leakage, contrast studies were routine together with ultrasonography and CT scanning. When anastomotic failure was confirmed the anastomosis was usually abandoned. The frequency of postoperative peritoneal sepsis increased with operative contamination (*Table 4*). The morbidity and mortality associated with reoperation increased with each procedure (*Figure 1*) and the importance of elimination of the source and avoidance of recontamination at the first procedure is clear.

Contamination of the peritoneal cavity and parietes by gastrointestinal content is the crucial factor in both wound and intraperitoneal sepsis after abdominal surgery. We think it possible that the high frequency of sepsis regularly reported in the context of antibiotic trials from the UK in recent years may reflect lapses in operative technique rather than ineffective antibiotics. Recognition that prophylactic antibiotics are effective (to a degree, obviously) may foster an uncritical attitude to the importance of technique—the avoidance of peritoneal and parietal contamination in particular. In addition, slavish adherence to scientific principle would have us abandon the simple, sensible and aesthetically pleasing use of wound towels and plastic ring wound protectors because they have not been shown scientifically to be of value. They do, however, minimize gross contamination of wound and parieties. We have become increasingly obsessional about avoidance of visible contamination in elective operations but at the same time believe that topical antibiotic lavage is likely to deal effectively with any that inadvertently occurs.

A relationship between surgical technique and outcome has been innate knowledge, although not often aired or apparently appreciated as an important variable in scientific studies. Now, however, the importance of technique as the main factor in surgical outcome is beginning to receive its due attention[16].

The onerous and obsessional collection of data during 10 years, together with its time-consuming analysis in this audit, begs the question of its value. It is certainly interesting and personally satisfying to have accurate information on surgical performance and the audit has also provided a ready source of information on management and outcome in various subgroups of patients[2,17–21]. In addition, awareness of critical audit of complications is undoubtedly a spur to maximum effort to avoid them: for example, antibiotic use becomes better defined and supervised, measures to avoid visible contamination at operation become more obsessional and any breach becomes an indication for immediate action. In terms of *improved* patient care, however, the benefit of this audit lacks tangibility. Resulting modifications in patient management have been limited to fairly small changes in antibiotic policy with statistically non-significant improvement in sepsis rates, except after highly selective vagotomy in which significant improvement occurred. Overall, we think that the considerable effort has been worth while but to continue in the same way has little appeal. A change to a microcomputer-based data collection system integrated into the clinical routine promises to make data collection easier although sophisticated manipulation of the information will continue to require computing expertise.

The value of audit as a potential source of improved patient care clearly depends on comparison of one surgical service with another within a hospital and ultimately in a wider national context. The dedication and work necessary in terms of documentation, data collection, validation and analysis to achieve meaningful information, even when limited to one area of interest such as wound infection, would, when extended to several consultants, be enormous. Such a development of audit is none the less desirable and is fuelled both by increasing awareness of variability in outcome and by the coincident increase in familiarity with, and availability of, computing facilities.

Currently, medical records and statistics are notoriously inaccurate[22,23] and reflect a general lack of interest in accurate documentation which the indiscriminate introduction of computing will not alter. Firm and continuing commitment by senior surgical staff is essential if data collection is to be accurate; the accumulation of large amounts of data of dubious accuracy and questionable relevance is an ever-present risk. The necessary and time-consuming validation of data, together with their analysis and presentation within a large hospital would inevitably require a central organization with expert staff. It is difficult and probably inappropriate to envisage individual clinicians devoting a large part of their time to such a task and the present ethos of the National Health Service is such that, without adequate financial support, a properly conducted wide-ranging surgical audit is a pipe dream.

Acknowledgements

We are grateful to Aberdeen University Computing Centre and Grampian Health Board for provision of computing facilities.

References

1 Condon RE, Nichols RL, Bartlett JG. Letter. *Am J Surg* 1986; **152**: 564.

2. Krukowski ZH, Stewart MPM, Alsayer HM, Matheson NA. Infection after abdominal surgery. five year prospective study *Br Med J* 1984; **288**: 278–80.

3 National Academy of Sciences–National Research Council. Division of Medical Sciences Ad Hoc Committee of the Committee on Trauma Postoperative wound infections, the influence of ultraviolet irradiation of the operating room and various other factors. *Ann Surg* 1964 (suppl 12).

4. Hewitt J, Reeve J, Rigby J, Cox AG. Whole gut irrigation in preparation for large bowel surgery. *Lancet* 1973, **ii**. 337–40.

5. Koruth NM, Krukowski ZH, Youngson GG *et al.* Intraoperative colonic irrigation in the management of left sided large bowel emergencies. *Br J Surg* 1985; **72**. 708–11.

6 Matheson NA. Single layer interrupted serosubmucosal anastomosis. In: Dudley HAF, ed. *Rob and Smith's Operative Surgery. Alimentary Tract and Abdominal Wall* 1, 4th ed London: Butterworths, 1983: vol. 1, 77–83

7. Krukowski ZH, Matheson NA. The management of peritoneal and parietal contamination in abdominal surgery. *Br J Surg* 1983; **70**: 440–1.

8. Krukowski ZH, Matheson NA. Acute diverticulitis. In: Russell RCG, ed. *Recent Advances in Surgery, Vol. 13.* Edinburgh Churchill Livingstone, in press

9. Cruse PJE, Foord R. The epidemiology of wound infection A ten year prospective study of 62,939 wounds. *Surg Clin North Am* 1980; **60**: 27–40

10. Condon RE, Bartlett JG, Greenlee H *et al.* Efficacy of oral and systemic antibiotic prophylaxis in colorectal operations *Arch Surg* 1983; **118**: 496–502.

11. McIlrath DC, Van Heerden JA, Edis AJ, Dozois RD. Closure of abdominal incisions with subcutaneous catheters *Surgery* 1976; **80**: 411–16

12. Keighley MRB, Burdon DW Letter *Am J Surg* 1986, **152**: 564–5

13. Lally KP, Trettin JC, Torma MJ Adjunctive peritoneal lavage in experimental peritonitis. *Surg Gynecol Obstet* 1983; **156**: 605–8

14 Steigbigel NH, Reed CW, Finland M. Susceptibility of common pathogenic bacteria to seven tetracycline antibiotics in vitro. *Am J Med Sci* 1968; **255**: 179–95

15. Krukowski ZH, Al-Sayer HM, Reid TMS, Matheson NA Effect of topical and systematic antibiotics on bacterial growth kinesis in generalized peritonitis in man. *Br J Surg* 1987, **74**. 303–6.

16. Russell RCG. Surgical technique *Br J Surg* 1987; **74** 763–4

17. Krukowski ZH, Koruth NM, Matheson NA. Evolving practice in acute diverticulitis. *Br J Surg* 1985, **72** 684–6.

18 Koruth NM, Hunter DC, Krukowski ZH, Matheson NA. Immediate resection in emergency large bowel surgery. a 7 year audit *Br J Surg* 1985; **72**: 703–7

19 Matheson NA, McIntosh CA, Krukowski ZH. Continuing experience with single layer appositional anastomosis in the large bowel. *Br J Surg* 1985 (suppl): s104–6

20. Krukowski ZH, Koruth NM, Matheson NA. Antibiotic lavage in emergency surgery for peritoneal sepsis *J R Coll Surg Edinb* 1986, **31**: 1–6.

21. Krukowski ZH, Cusick EL, Engeset J, Matheson NA Polydioxanone or polypropylene for closure of midline abdominal incisions. a prospective comparative clinical trial *Br J Surg* 1987; **74** 828–30.

22 Whates PD, Birzgalis AR, Irving M. Accuracy of hospital activity analysis codes. *Br Med J* 1982, **284**: 1857–8.

23 Crawshaw C, Moss JG. Accuracy of hospital activity analysis operation codes *Br Med J* 1982, **285**: 210

Paper accepted 3 May 1988

Br. J. Surg. 1988, Vol. 75, September, 862–865

Pyogenic liver abscess: an improvement in prognosis

O. Farges, T. Leese* and H. Bismuth

*The Hepatobiliary Unit, Hôpital Paul Brousse, Villejuif, France and * Department of Surgery, University of Leicester, Leicester, UK*

Correspondence to: Professor H. Bismuth, Chirurgie Hépato-Biliaire, Hôpital Paul Brousse, 14 avenue Paul Vaillant Couturier, 94800 Villejuif, France

Forty-six patients with pyogenic liver abscess have been treated at Paul Brousse Hospital between 1966 and 1986. The overall mortality was 24 per cent, all 11 deaths occurring in 24 patients seen prior to 1978 when there was often a considerable delay in the diagnosis of liver abscess (mean 90 ± 71 days). In seven patients the diagnosis was not made until post-mortem examination. The mainstay of treatment was surgical drainage. Since 1978 high resolution imaging techniques for the liver, and in particular ultrasound, have been available. The diagnostic delay has been significantly reduced (mean 28 ± 20 days, $P < 0.01$*). Patients are receiving definitive treatment at an earlier stage in the evolution of the disease process, with fewer established complications prior to treatment (*$P < 0.05$*). Percutaneous drainage under ultrasound control is the preferred initial drainage procedure in high-risk patients. There have been no deaths in 22 patients treated for pyogenic liver abscess since 1978 (*$P < 0.001$*).*

Keywords: Liver, liver abscess, ultrasound diagnosis, percutaneous drainage

Historically pyogenic liver abscess has been associated with high morbidity and mortality rates[1]. The introduction of antibiotics and advances in bacteriology and diagnostic techniques have generally improved the outcome, but mortality rates of 40–80 per cent are still reported[2–7]. Delayed and missed diagnosis has been prominent[7–9]. A basic requirement for effective therapy is early diagnosis[8]. This has been made easier with the introduction of high resolution imaging techniques including ultrasound and computed tomography (CT). Some patients, if diagnosed early, will respond to medical treatment alone in the form of diagnostic percutaneous aspiration and effective antibiotic therapy[10–14]. Most cases require drainage of the abscess. Surgical drainage has allowed considerable improvement in prognosis, but mortality following surgical drainage still averages 20 per cent[4,6,15]. The wider use of percutaneous drainage under ultrasound or CT control has been proposed[4].

The indications and relative merits of surgical and percutaneous drainage are difficult to assess from the literature. Only 11 studies report the use of percutaneous drainage of pyogenic liver abscess in more than five patients[16–26]. Most come from departments of radiology and do not assess the severity of the patient's condition, nor define the relative indications for percutaneous and surgical drainage. Where comparison is made to the surgically treated patient, these are usually historical controls prior to the availability of high resolution imaging techniques. Only two studies have tried to compare percutaneous and surgical drainage in patients treated in the same institution during the same period[17,23]. The results were detailed in one study[17] in which no difference was demonstrable in morbidity, mortality or the need for further drainage procedures between the groups. A prospective controlled trial is not feasible as percutaneous and surgical drainage are complementary procedures, the relative merits of which must be assessed in individual patients.

Our treatment of pyogenic liver abscess has evolved since 1978. This study was undertaken to assess the effect of the introduction of ultrasound scanning in the diagnosis and monitoring of liver abscess and to help define the indications for ultrasound-guided percutaneous drainage and surgical drainage in the current approach to therapy.

Patients and methods

The hospital records and morphological examinations of all patients seen at the Paul Brousse Hospital with hepatic abscess from 1966 to 1986 inclusive were reviewed. This included a review of all autopsy reports during this period. Patients were included in the study when they had acute pyogenic abscess confirmed by the presence of pus within the cavity at aspiration, drainage or post-mortem examination Patients were excluded if they had received treatment for their abscess at another hospital prior to referral or when the abscess was chronic or the result of trauma or superinfection of a pre-existing cyst or tumour. Amoebic abscess or other specific infections such as actinomycosis and brucellosis were also excluded.

The diagnostic delay was defined as the time between the onset of symptoms retrospectively attributable to the abscess and the diagnosis Abscesses were labelled cryptogenic when no causative lesions could be demonstrated. The diagnostic accuracy of morphological investigations was defined as their ability to identify all hepatic lesions correctly.

Important changes in the diagnosis and treatment of pyogenic liver abscess occurred during the study period. From 1966 to 1977 plain abdominal X-ray, radioisotope liver scan and arteriography were the principal imaging methods for the diagnosis of liver abscess, supplemented when necessary by diagnostic percutaneous aspiration. All patients were treated with antibiotics usually followed by transperitoneal surgical drainage, except in the most severely ill patients in whom percutaneous drainage was attempted, guided by diagnostic aspirations.

Since 1978 ultrasound has been the principal examination used in the diagnosis and monitoring of liver abscesses. Initial diagnostic percutaneous aspiration under ultrasound control enables an assessment of the viscosity of the pus and bacteriological examination. Targeted antibiotic therapy is then commenced, but when symptoms do not resolve within 24 h the abscesses are drained. Percutaneous drainage under ultrasound control is now performed in the majority of cases, either as a preliminary procedure or as the definitive treatment, particularly in high-risk patients. Surgical drainage as the initial procedure is reserved for low-risk patients with an associated intra-abdominal pathology requiring surgery or with viscid pus or a thick-walled abscess cavity as assessed at diagnostic percutaneous aspiration.

Surgical and percutaneous drainage procedures are performed by the same surgical team Surgical drainage is achieved by the transperitoneal route. The site and size of abscesses were confirmed by palpation and needle aspiration, but since 1985 operative ultrasonography has been used to locate the abscesses accurately and choose a site to traverse the liver parenchyma avoiding major vascular and biliary structures Large silicone drains (30 F or greater) are positioned in the cavities following surgical drainage. We do not use irrigation techniques or omental packing to manage the residual cavity. Percutaneous drainage since 1978 has been performed under local anaesthetic after locating a guide wire in the cavity under ultrasound control Over-the-wire dilators are then used to create a tract large enough to accept 10–16 F drains Following both types of drainage procedure, drains are withdrawn only after complete disappearance of the cavity as assessed by serial ultrasound examinations and/or sinography over a period of several weeks

0007–1323/88/090862–04$3 00

Table 1 *Comparison of patient characteristics in Groups 1 and 2*

	Group 1 (1966–1977) $n=24$	Group 2 (1978–1986) $n=22$
Male/female	8/16	14/8
Age (years, mean±s.d.)	46·9±18·3	56·0±16·5
Aetiology:		
Biliary (neoplastic)	12 (6)	9 (5)
Septicaemic	7	7
Portal	1	2
Contact	1	0
Cryptogenic	3	4
Multiple abscesses (%)	50	54·5
Diameter of abscesses* (cm, mean±s.d.)	8·0±2·7	7·2±2·6
Fever >39°C (%)	71	73
WBC $>12\times10^9$/litre (%)	75	77
Positive blood culture (%)	55	57
Positive abscess culture (%)	69	75

* Excluding multiple small abscesses <2 cm diameter

Major risk factors regarded as contra-indications to surgical drainage were septic shock with multi-organ failure. Moderate risk factors regarded as relative contra-indications to surgical drainage were the presence of weight loss >10 kg, serum albumin <30 g/litre, respiratory or renal failure or septic shock.

All patients were followed up for at least 6 months after discharge from hospital (range 6 months–5 years). Statistical analysis of results was performed using the χ^2 test (±Yates' correction) for clinical variables and Mann–Whitney ranking test for continuous parameters.

Results

Forty-six patients with pyogenic liver abscess were studied. There were 22 men and 24 women with a mean age of 51±17 years. The probable route of infection was biliary in 21, septicaemia in 14, portal in 3 and direct spread from an adjacent pyogenic focus in 1. The remaining 7 patients had no obvious primary source of infection (cryptogenic).

An associated primary intra-abdominal pathology warranting surgery was found in 27 of the 46 patients (59 per cent) as follows: biliary obstruction (20), peritonitis (4), diverticulitis (2), cholecystitis (1). Eleven of these patients underwent simultaneous surgical treatment of their primary pathology and liver abscesses. Three patients with neoplastic biliary obstruction associated with cholangitis and multiple liver abscesses were treated by percutaneous drainage. Seven patients died without treatment of their primary pathology (in two the liver abscess had been drained percutaneously prior to death and in five the liver abscesses were only diagnosed at post-mortem examination). In the remaining six patients the treatment of the primary abdominal pathology was delayed for an average of 3 months after percutaneous drainage (5) or medical treatment (1) of the liver abscesses. The primary pathologies were biliary obstruction (3), acute diverticulitis (2) and acute cholecystitis (1). In none of these patients did the abscesses recur between the two treatments.

The commonest presenting symptoms attributable to the liver abscesses were weight loss, abdominal pain and rigors. Fever was common and 33 patients (72 per cent) had a temperature >39°C. The liver was usually tender and/or enlarged. Liver function tests were deranged with raised serum bilirubin in over half the patients, a figure biased by the large number of patients with a primary biliary pathology. The white blood count was $>12\times10^9$/litre in 76 per cent of patients. Blood cultures were positive in 56 per cent and culture of the pus from the abscess was positive in 72 per cent, both despite many patients having received 'blind' antibiotic therapy before referral. The bacteria most frequently isolated were *Escherichia coli*, *Streptococcus fecalis*, micro-aerophilic and anaerobic streptococci and *Pseudomonas*. Pus from 10 abscesses grew multiple organisms. The major changes in antibiotic therapy which occurred during the study period were the increasing use of cephalosporins and metronidazole.

The sensitivity of ultrasound in detecting liver abscesses was 86 per cent, which was greater than radio-isotope liver scan (48 per cent) or arteriography (74 per cent). Abscesses were multiple in 52 per cent of patients. Excluding multiple small abscesses, the mean diameter of abscesses was 7·6±2·6 cm.

In four patients the liver abscesses responded to medical treatment alone (diagnostic aspiration and antibiotic therapy). Fourteen patients were treated by percutaneous drainage and 21 patients were treated by surgical drainage. In the remaining seven patients the liver abscesses were not diagnosed until post-mortem examination. Duration of drainage and hospital stay were similar following percutaneous and surgical drainage. Overall mortality was 24 per cent. The incidence of complications following percutaneous and surgical drainage was not statistically different (20 per cent *versus* 29 per cent).

A second drainage procedure was required in seven patients (20 per cent). This was because of the presence of additional abscesses not communicating with the drains, a thick-walled abscess or viscous pus and necrotic debris blocking the drains. A second procedure was required in 5/14 patients who had undergone percutaneous drainage (36 per cent) and 2/21 patients who had undergone surgical drainage (9·5 per cent, $P<0\cdot05$).

Twenty-four patients were admitted between 1966 and 1977 (Group 1) and 22 patients were admitted after the introduction of ultrasound scanning in 1978 (Group 2). The two groups were well matched in terms of the aetiology and severity of their abscesses, though there was a larger proportion of males in Group 2 (*Table 1*). The mean diagnostic delay in Group 1 was 90±71 days, while in Group 2 it was only 28±20 days ($P<0\cdot01$). In seven patients in Group 1 the diagnosis of liver abscess was not made until post-mortem examination, while in no patient in Group 2 was the diagnosis delayed until post-mortem ($P<0\cdot02$). The increased diagnostic delay is reflected in the frequency of established complications in patients at the time of treatment (*Figure 1*). In Group 1 10/17 patients (59 per cent) were judged moderate or major risk at the time of drainage of which four subsequently died. In Group 2 6/22 patients

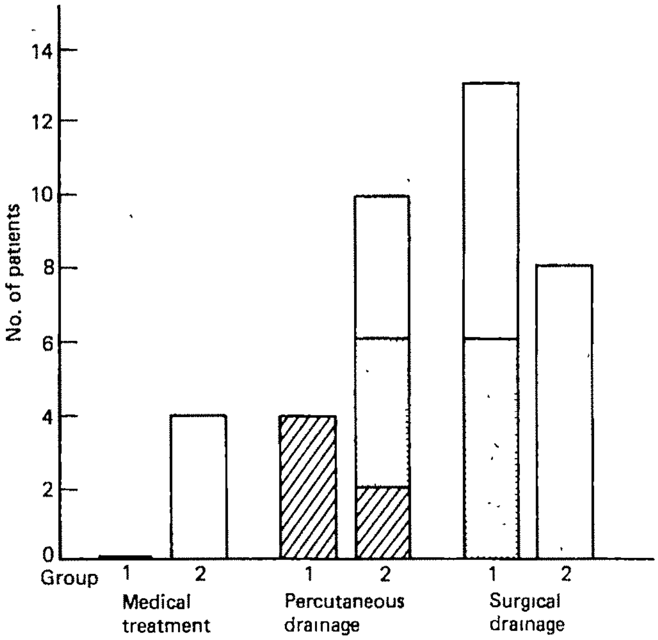


Figure 1 *Treatment methods subdivided according to severity of complications at the time of treatment and the patient group, Group 1 = 1966–1977; Group 2 = 1978–1986.* □, *low-risk patients*, ▨, *moderate-risk patients*; ■, *high-risk patients*

(27 per cent) were judged moderate or major risk at the time of treatment and there were no deaths.

The type of treatment also altered after 1978 (*Figure 1*). Four patients responded to medical treatment alone and more patients were treated by initial percutaneous drainage under ultrasound control. Initial surgical drainage was used only for some low-risk patients, particularly when there was associated primary intra-abdominal pathology requiring surgery.

The overall mortality in Group 1 was 46 per cent (11/24). There were no deaths in Group 2 ($P < 0.001$). There was a reduction in the incidence and severity of complications with time in both percutaneously and surgically treated patients. The overall incidence of complications was reduced from 49 per cent in Group 1 to 9 per cent in Group 2.

Discussion

Prior to the introduction of high resolution imaging techniques, 30–50 per cent of liver abscesses were not diagnosed until post-mortem examination[4,5,7,23], as confirmed by our experience prior to 1978. The improved diagnostic accuracy permitted by imaging techniques such as ultrasound and CT has undoubtedly contributed in a major way to the reduction in mortality and morbidity, as demonstrated by Gerzof *et al.*[18] in a review of the recent literature. Ultrasound and CT scans have several other advantages in that they provide accurate information on the topography, size, number and extent of the abscesses. Ultrasound is readily available and can be performed even in acutely ill patients without delay—at the bedside if necessary.

The significant reduction in diagnostic delay is associated with an improvement in the general condition of the patients at the time of treatment. Fewer patients have experienced septic shock, major organ failure, significant weight loss or hypoalbuminaemia prior to therapy. Targeted antibiotic therapy can be commenced earlier based on culture of organisms from the pus, thus replacing 'blind' antibiotic therapy which may be ineffective and lead to bacterial resistance.

Although medical treatment alone is effective in a minority of patients[10–14], drainage of the abscess remains the mainstay of treatment. In choosing between surgical and percutaneous drainage several factors must be considered including the anaesthetic risk posed by the patient, the presence or absence of a coexisting primary intra-abdominal pathology warranting surgery, the relatively limited size of the drains that can be introduced percutaneously, the complications and failure rates of the two procedures, and the local expertise.

Percutaneous drainage under ultrasound control is the treatment of choice in the critically ill patient in whom general anaesthetic and surgery might prove fatal. Although of considerable benefit, percutaneous drainage is not necessarily the best treatment for all patients. It is associated with a significantly higher failure rate than surgical drainage[18] (36 per cent versus 9·5 per cent in this series). This may be due to the limited size of drainage tubes that can be introduced percutaneously, particularly if the pus is viscid with necrotic debris within the cavity. The use of larger percutaneous drains and irrigating catheters may improve the results. Surgical drainage of liver abscesses still has a place in low-risk patients, particularly when there is an associated intra-abdominal pathology requiring surgery, the pus is viscid or the abscess cavity thick-walled, or where percutaneous drainage has failed. We experienced no deaths in these groups of patients treated surgically and hospital stay was similar to that following percutaneous drainage. Up to 50 per cent of patients with pyogenic liver abscess may therefore still be better treated by surgical drainage[2,4,6,23,27].

The choice of treatment in cases of multiple or multiloculated abscesses is controversial. Surgical drainage of multiple abscesses has been associated with a high mortality[2,4,6] but this may be because of difficulty locating multiple abscesses by simple palpation at laparotomy. Most patients were treated before the availability of high resolution imaging techniques to localize the abscesses pre-operatively. We would now advocate peroperative ultrasound for the accurate localization of all abscesses at laparotomy[28]. In this study the prognosis associated with multiple abscesses was no worse than for solitary abscesses. Medical treatment alone is adequate for some patients with multiple small abscesses. There is frequently a communication between multiple and multiloculated[18] abscesses, either direct or via the biliary tree. Effective drainage can often be achieved through a single drain placed percutaneously or surgically.

This study clearly demonstrates an improvement in the prognosis of pyogenic liver abscess in recent years, the mortality falling from 46 per cent prior to 1978 to 0 per cent in the period 1978–1986. This improvement appears to be principally the result of earlier diagnosis allowing more opportune treatment. More effective antibiotic therapy and the introduction of ultrasound or CT-guided percutaneous drainage are important advances. The selection of surgical or percutaneous drainage should be based on a careful assessment of each patient.

References

1. Ochsner A, De Bakey M, Murray S. Pyogenic abscess of the liver. *Am J Surg* 1938; **40**, 292–319.

2. Pitt HA, Zuidema GD Factors influencing mortality in the treatment of pyogenic hepatic abscess. *Surg Gynecol Obstet* 1975; **140**· 228–34.

3 Barbour GL, Juniper K. A clinical comparison of amebic and pyogenic abscess in the liver in sixty-six patients. *Am J Med* 1972, **52**: 323.

4. Neoptolemos JP, Macpherson DS, Holm J, Fossard DP. Pyogenic liver abscess. a study of forty-four cases in two centres *Acta Chir Scand* 1982; **148**; 415–21.

5 Northover JMA, Jones BJM, Dawson JL, Williams R. Difficulties in the diagnosis and management of pyogenic liver abscess. *Br J Surg* 1982; **69**: 48–51.

6. Miedema BW, Dineen P. The diagnosis and treatment of pyogenic liver abscesses. *Ann Surg* 1984; **200**: 328–35.

7. Rubin RH, Swartz MN, Malt R. Hepatic abscess: changes in clinical, bacteriological and therapeutic aspects. *Am J Med* 1974; **57**· 601–10.

8 Silver S, Weinstein A, Cooperman A. Changes in the pathogenesis and detection of intrahepatic abscess. *Am J Surg* 1979; **137**· 608–10

9. Butler TJ, McCarthy CF. Pyogenic liver abscess. *Gut* 1969; **10**: 398–9.

10 Berger LA, Osborne DR Treatment of pyogenic liver abscesses by percutaneous needle aspiration. *Lancet* 1982; **i**: 132–4

11 Dietrick RB Experience with liver abscesses. *Am J Surg* 1984; **147** 288–91.

12. Herbert DA, Fogel DA, Rothman J, Wilson S, Simmons F, Ruskin J. Pyogenic liver abscesses: successful non-surgical therapy. *Lancet* 1982, **i**· 134–6.

13. Maher JA, Reynolds TB, Yellin AE. Successful medical treatment of pyogenic liver abscess. *Gastroenterology* 1979; **77**: 618–22

14. Perera MR, Kirk A, Noone P. Presentation, diagnosis and management of liver abscess *Lancet* 1980; **ii**: 629–32

15. Kayabali I, Yilmaz D, Gurel M Solitary pyogenic liver abscess· a statistical analysis of 117 cases. *Int Surg* 1983; **68**: 149–50.

16. Bernardino ME, Berkman WA, Plemmons M, Sones PJ, Price RB, Casarella WJ Percutaneous drainage of multi-septated hepatic abscess. *J Comput Assist Tomogr* 1984; **8**: 38–41.

17. Bertel CK, Van Heerden JA, Sheedy PF Treatment of pyogenic hepatic abscesses. Surgical versus percutaneous drainage *Arch Surg* 1986, **121**: 554–8.

18. Gerzof SG, Johnson WC, Robbins AH, Nabseth DC. Intrahepatic pyogenic abscesses: treatment by percutaneous drainage. *Am J Surg* 1985; **149**: 487–94

19. Gobien RP, Young JWR, Curry NS, Gobien BS, Valicenti JR, Reines HD Computed tomographic guidance of percutaneous needle aspiration and drainage of abdominal abscesses. *J Comput Assist Tomogr* 1982, **6**: 127–33.

20. Haaga JR, Weinstein AJ CT-guided percutaneous aspiration and drainage of abscesses. *AJR* 1980; **135**: 1187–94

21. Karlson KG, Martin EC, Fankuchen EI, Shultz RW, Casarella

WJ. Percutaneous abscess drainage. *Surg Gynecol Obstet* 1982; **154**: 44–8.
22. Kuligowska E, Connors SK, Shapiro JH. Liver abscess: sonography in diagnosis and treatment. *AJR* 1982, **138**: 253–7
23. MacDonald MI, Corey GR, Gallis HA, Durack DT. Single and multiple pyogenic liver abscesses. Natural history, diagnosis and treatment with emphasis on percutaneous drainage. *Medicine* 1984; **63**· 291–302.
24. Mandel SR, Boyd D, Jaques PF, Mandel V, Staab EV. Drainage of hepatic, intraabdominal and mediastinal abscesses guided by computerized axial tomography. *Am J Surg* 1983, **145**: 120–5.
25 Scheinfeld AM, Steiner AE, Rivkin LB, Dermer RH, Shemesh OV, Dolberg MS. Transcutaneous drainage of abscesses of the liver guided by computed tomography scan. *Surg Gynecol Obstet* 1982; **155**: 662–6.
26 Van Sonnenberg E, Ferruci JT, Mueller PR, Wittenberg J, Somone JF, Malt RA Percutaneous radiographically guided catheter drainage of abdominal abcesses. *JAMA* 1982; **247**: 1090–2.
27. Heymann AD Clinical aspects of grave pyogenic abscesses of the liver. *Surg Gynecol Obstet* 1979, **149**: 209–13
28. Bismuth H, Castaing D. *Intraoperative Sonography of the Liver and Biliary Tract*. Berlin: Springer–Verlag, 1987

Paper accepted 23 May 1988

Short note

Br. J. Surg. 1988, Vol. 75, September, 865

Pulsatile varicose veins

R. L. Blackett and G. E. Heard

University Hospital of Wales, Cardiff CF4 4XW, UK
Correspondence to: Mr R. L. Blackett

The clinical findings of elevated jugular venous pressure, hepatomegaly, peripheral oedema and ascites in patients with cardiac failure and tricuspid regurgitation are well recognized[1]. However, the pulsation of ventricular systole may be conducted to the long saphenous system of the lower limb if there is saphenofemoral incompetence and the cause of this pulsation may not immediately be recognized. We report two cases which presented to general surgeons and which demonstrate a potential pitfall for the unwary.

Case reports

Case 1

A 54-year-old lady had noticed a painful swelling in the left groin for several weeks. This increased in size on standing and softened on lying down. She had long-standing rheumatic heart disease and had undergone a mitral valvotomy 20 years previously and a mitral valve replacement and tricuspid annuloplasty the previous year. Cardiac catheterization had been performed only via the right groin but she did recall having had blood samples taken from the left groin.

On physical examination the swelling in the groin was found to be a varix with gross dilatation throughout the long saphenous system. The striking feature of these varicosities was marked expansile pulsation. An arteriovenous fistula was suspected but careful examination throughout the limb and groin revealed no machinery murmur. Limb length was symmetrical, which would not have been the case had there been a congenital arteriovenous communication.

Further examination revealed evidence of cardiac failure. Her jugular venous pressure was elevated to the angle of the jaw and her liver was enlarged. Despite the tricuspid annuloplasty she had gross tricuspid regurgitation and this was the cause of the pulsating varicose veins.

Discussion of this patient with colleagues then brought to light a similar case that had presented 10 years earlier (Case 2)

Case 2

A 41-year-old lady had had rheumatic fever and chorea as a child. She had undergone mitral valve replacement 6 years before she presented to the surgical clinic. Following this operation she had been well with reduction in lower limb oedema and improved exercise tolerance. However, she had developed gross varicose veins in her left leg.

Physical examination revealed gross varicosities of the left long saphenous system. On closer inspection these varicosities exhibited prominent expansile pulsation. She had previously undergone cardiac catheterization via the left groin and it was initially suspected that the pulsation in the varicose veins was the result of an arteriovenous fistula.

A decision was made to explore the groin. At operation a large pulsating long saphenous vein was exposed. All structures between the femoral artery and femoral vein were divided including a fibrous band which was considered to be a possible communication. Despite this, pulsation persisted in the varicose veins. It was then realized that the pulsation was the result of tricuspid regurgitation. Saphenofemoral ligation was performed.

Discussion

It is well established that gross tricuspid regurgitation produces a prominent 'V' wave in the jugular venous pulse This represents the pressure wave of right ventricular systole transmitted through the incompetent tricuspid valve. The physical signs of tricuspid regurgitation resolve when cardiac failure is treated and the degree of tricuspid incompetence is reduced.

In the two patients described, the prominent 'V' wave seen in the jugular veins was also present in lower limb varicose veins as a result of valvular incompetence at the saphenofemoral junction. Such pulsating varicose veins have previously been described in association with tricuspid regurgitation in medical textbooks[2] and reviewed in the literature[3]. When they are seen in a surgical clinic, however, attention may be directed to the diagnosis of local and surgical causes of venous pulsation such as arteriovenous fistula. Such a diagnosis is not unreasonable if cardiac catheterization or venepuncture have been performed. On clinical grounds it should be possible to exclude an arteriovenous fistula if the characteristic machinery murmur is absent.

These two cases demonstrate that if pulsating varicose veins are seen, a cardiac cause may easily be overlooked and invasive investigative or even surgical procedures performed before the correct diagnosis is reached.

References

1 Cha SD, Gooch AS Diagnosis of tricuspid regurgitation Current status. *Arch Intern Med* 1983; **143**: 1763–8.
2 Friedberg CK. *Diseases of the Heart*. 3rd ed Philadelphia and London: W.B. Saunders, 1966: 1167.
3 Brickner PW, Scudder WT, Weinrib M. Pulsating varicose veins in functional tricuspid insufficiency. Case report and venous pressure tracing. *Circulation* 1962; **25**: 126–9

Paper accepted 12 April 1988

Br. J. Surg. 1988, Vol. 75, September, 866–868

Anterior lesser curve seromyotomy and posterior truncal vagotomy for chronic duodenal ulcer: the results at five years

A. K. Siriwardena and A. A. Gunn

Department of Surgery, Bangour General Hospital, Dechmont, Broxburn, West Lothian EH52 6LR, UK

Correspondence to:
Mr A. K. Siriwardena, 32 Long Crook, South Queensferry EH30 9XR, UK

In one surgical unit, 241 patients have undergone anterior gastric seromyotomy and posterior truncal vagotomy for chronic duodenal ulcer. The postoperative mortality rate was 0·4 per cent. Four patients (1·6 per cent) required a drainage procedure for gastric stasis. The first 66 patients (Group A) were followed prospectively and 58 were available for assessment at 5 years. Eight patients (14 per cent) had developed a recurrent ulcer. In seven of these patients this responded to conservative treatment with H_2 receptor antagonists. One patient has required Polya partial gastrectomy for recurrent ulceration. At 5 years 47 patients (81 per cent) were placed in the Visick I or II categories. In the next 175 patients (Group B), the ulcer recurrence rate was 3 per cent, suggesting a learning curve in mastering the procedure. We conclude that the immediate and 5-year results of the first 66 patients are at least comparable with those of highly selective vagotomy. Anterior gastric seromyotomy with posterior truncal vagotomy is an easy and rapid procedure and may be more widely applicable than highly selective vagotomy.

Keywords: Duodenal ulcer, seromyotomy, ulcer recurrence

Elective peptic ulcer surgery retains a place in current surgical practice[1]. The operation of highly selective vagotomy is technically complex and has a high reported long-term ulcer recurrence rate in some series[2]. The operation of anterior lesser curve seromyotomy with posterior truncal vagotomy has been developed as an alternative pylorus-preserving operation in which the parietal cell mass is denervated[3]. The operation appears to be safe and is relatively simple and speedy to perform[4]. Initial reports[5,6] suggest a low incidence of immediate postoperative complications, but long-term follow-up is essential before more widespread adoption of this procedure.

We present here a detailed prospective 5-year follow-up study of 66 patients (Group A) who have undergone this procedure, together with the short-term results obtained in a further 175 patients (Group B).

Patients and methods

In the 6-year period January 1980 to December 1985, 241 patients referred for surgical treatment of endoscopically confirmed duodenal ulcer underwent anterior gastric seromyotomy with posterior truncal vagotomy (AGM + PTV). Criteria for exclusion were the presence of pyloric stenosis and emergency presentation with bleeding or perforation No patients were excluded on the grounds that technical difficulty was anticipated or because of obesity.

Group A

The first 66 patients undergoing the operation (up to December 1981) were followed prospectively. Their mean age at the time of surgery was 39·9 years, and 61 per cent of them were male. An insulin secretion test was performed during the third postoperative month; the results have been published elsewhere[7].

Patients were reviewed postoperatively at 1 month, 3 months, and 1 year, and then annually for 5 years. Review was carried out by surgical unit staff of consultant or registrar grade A card was attached to the inside front cover of the case notes This contained a list of the important postvagotomy symptoms, namely pain, nausea, food vomiting, bile vomiting, flatulence, heartburn, waterbrash, dumping, diarrhoea, dysphagia, distension and weight change. The term 'dumping' was taken to include early and late forms, and refers to symptoms attributed to uncontrolled rapid gastric emptying The patient's weight was recorded at each visit and patients were asked to report any symptoms and asked specifically about those listed above. The aim of this standardized approach was to ensure that no important symptoms were missed and to minimize the unavoidable inconsistencies that arise when patients are reviewed by different members of staff. The Visick classification as modified by Goligher *et al.*[8] was used to categorize patients. Further enquiry was made in the case of patients not in Visick grade 1 to ascertain what proportion of their symptoms had been present pre-operatively, and what proportion were new and therefore possibly attributable to their operation The Visick status at 5 years was recorded by the clinician making this final assessment. Endoscopy was used to diagnose all recurrent ulcers.

Group B

The next 175 patients underwent surgery between January 1982 and December 1985. These operations were carried out by consultants (110 patients), by senior registrars (45), and by registrars under supervision (20). Eight patients in this group underwent cholecystectomy at the same time as AGM + PTV, and a further four underwent Nissen fundoplication at the same time as AGM + PTV. Patients in this group were followed prospectively for a median period of 6 months (range 3–48 months). A review of the updated entries in their case records was carried out in January 1987 to determine how many of this group had been referred back to our unit with complications of surgery or suspected recurrent ulcers

The third part of our study consisted of an overview of patients in both groups ($n = 241$) to establish the operating time, operative mortality and immediate postoperative complications of AGM + PTV. Operating time was defined as the time from induction of anaesthesia to the return of the patient to the recovery room. Operative mortality was defined as death occurring during surgery or the subsequent 30 days. The term 'immediate postoperative complications' refers to problems occurring from the time of the return of the patient to the recovery room to discharge from hospital. The figures for operating time were available for 178 of the 241 patients. We then compared these figures with the operating times for a series of 200 patients who had undergone a standard truncal vagotomy and pyloroplasty in the same surgical unit. The two groups were not age and sex matched, but the same criteria were used to define operating time, and the operations were carried out or supervised by the same consultant, with a similar percentage being carried out by junior staff

0007–1323/88/090866–03$3 00

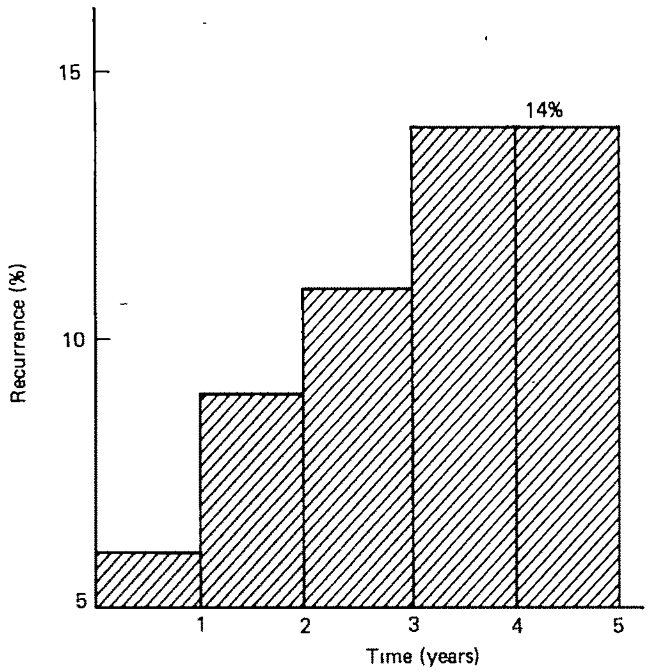


Figure 1 *Cumulative ulcer recurrence rate in 58 Group A patients available for follow-up after anterior gastric seromyotomy and posterior truncal vagotomy*

When assessing postoperative morbidity after AGM+PTV, atelectasis was diagnosed on clinical grounds by finding evidence of segmental collapse or consolidation. Positive sputum culture, leucocytosis and radiological changes on chest X-ray were used to support the diagnosis. Wound infection was defined as erythema or discharge. Doppler studies were used to confirm suspected deep vein thrombosis, and pulmonary embolism was diagnosed by a combination of clinical examination, chest radiograph, ECG and arterial blood gas analysis. Ileus was classified as prolonged if it was present for >4 days.

Results

Group A

Of the original group of 66 patients, 58 were available for review at five years (88 per cent follow-up). Four patients were lost to follow-up and four patients had died. The causes of death and the interval in months after undergoing AGM+PTV were as follows:

(1) haemorrhage from a retroperitoneal sarcoma at 32 months,
(2) metastatic disease from a primary colonic carcinoma at 55 months,
(3) metastatic disease from an unknown primary at 32 months,
(4) acute myocardial infarction at 42 months.

None of these deaths was related to complications of peptic ulcer disease or to the original operation.

With regard to Visick grading, 31 of the 58 (53 per cent) patients were categorized in grade I, 16 (28 per cent) in grade II, 3 (5 per cent) in grade III and 8 (14 per cent) in grade IV. The 16 patients allocated to Visick grade II were all recorded as being satisfied with the results of their surgery. They suffered occasional minor symptoms only and endoscopy had not been considered necessary. The three patients allocated to Visick grade III underwent endoscopy but this showed no abnormality in all cases.

Eight patients (14 per cent) had a recurrent ulcer confirmed at endoscopy. The cumulative ulcer recurrence rate is shown in *Figure 1*. Seven of these patients were treated conservatively with a course of H_2 receptor antagonists. Repeat endoscopy was carried out and confirmed ulcer healing at 6 weeks in all seven patients. The eighth patient presented with two large recurrent ulcers on the anterior and posterior walls of the first part of the duodenum and was treated surgically by Polya partial gastrectomy.

The results of the 27 patients not in the Visick category I were further analysed (*Table 1*) to see what proportion of their symptoms had been present pre-operatively. The patient with a surgically treated recurrent ulcer was allocated to the Visick grade IV by convention, although according to symptoms present at 5 years this patient would have been placed in the Visick grade II. However, this patient is excluded from the analysis in *Table 1* as the purpose of this analysis was to see which symptoms could be attributed to the operation of AGM+PTV.

Group B

At review in January 1987 the ulcer recurrence rate in these 175 patients was 3 per cent as confirmed by endoscopy. A further four patients presented with symptoms of persistent gastric stasis. Outflow obstruction without recurrent ulcer was the diagnosis established by a combination of endoscopy and barium studies. Endoscopic dilatation of the pylorus[9] was not used, and all four were treated surgically by retrocolic gastrojejunostomy with relief of symptoms in all cases.

Overview of all patients

The complete series of 241 patients was examined. The operating times are recorded in *Table 2*. There was one death in the postoperative period (mortality rate 0·4 per cent). A post-mortem examination revealed that the cause of death was an acute myocardial infarction. The frequency of immediate postoperative complications is seen in *Table 3*. In two patients the notes record the prolonged absence of bowel sounds without evidence of peritonism or constitutional upset, and a diagnosis of prolonged ileus was made. However in both cases this settled spontaneously on the fifth and sixth postoperative day respectively. A further patient was recorded as developing the symptoms and signs of 'subacute' small bowel obstruction on the fifth postoperative day. However, a Gastrografin swallow showed rapid transit of contrast into the large bowel and the patient was treated conservatively. The symptoms settled within 24 h. Postoperative leakage from the myotomy site requiring surgical intervention did not occur. The average length of stay in hospital was 7 days.

Table 1 *Analysis of patients from group A with symptoms at five years* ($n=26$)

Symptoms	Present at 5 years	Present before operation	New symptom
Nausea	8	6	2
Vomiting	3	3	0
Distension	12	5	7
Heartburn	17	15	2
Waterbrash	10	7	3
Flatulence	11	6	5
Pain	9	9	0
Dumping	1	0	1
Diarrhoea	2	0	2

Table 2 *Operating time for anterior gastric seromyotomy and posterior truncal vagotomy (AGM+PTV) and truncal vagotomy and pyloroplasty (TV+P)*

	Operating time (min)	
Grade of operator	AGM+PTV ($n=178$)	TV+P ($n=200$)
Registrar or senior registrar	80 (60–105)	90 (45–110)
Consultant	52 (40–80)	70 (40–80)

Values are medians with ranges in parentheses

Table 3 *Immediate postoperative complications after AGM + PTV*

Complication	No. of patients
Atelectasis	120 (50)
Wound infection	10 (4)
Wound dehiscence	1 (0·4)
Urinary retention	27 (11)
DVT	2 (0·8)
Pulmonary embolus	2 (0·8)
Prolonged ileus (>4 days)	2 (0·8)
Intestinal obstruction	1 (0·4)
Leaks	0
Dysphagia	1 (0·4)
No complications	82 (34)

Figures in parentheses are percentages

Discussion

In this series of 241 patients the operative mortality rate was 0·4 per cent, and as the one death was due to an acute myocardial infarction it is unlikely to have been related to the particular type of ulcer operation performed. The recorded operating times show that AGM + PTV is an acceptably quick procedure. Postoperatively, one-third of patients had no complications, and the commonest complication was atelectasis (*Table 3*). No patient required re-operative surgery for complications during the immediate postoperative period. The specific complication of lesser curve necrosis described after highly selective vagotomy[10] did not occur in our series.

In the prospective study (Group A), the recurrent ulcer rate of 14 per cent at 5 years compares favourably with the reported ulcer recurrence rates after highly selective vagotomy[11,12]. Although most recurrences occurred within the first 2 years it is known that there is a gradual rise in the cumulative ulcer recurrence rate after HSV for at least 10–15 years[2], and the same may apply to AGM + PTV. Over half of our patients (53 per cent) were asymptomatic at 5 years and 81 per cent were in the Visick I or II categories and were satisfied with the results of their surgery. Eight patients were placed in the Visick grade IV on the basis of proven recurrent ulceration. However, when they were assessed at 5 years, one was asymptomatic and a further five had minimal symptoms and would have been placed in the Visick II category had they not by convention been retained in category IV.

At five years, 27 patients had symptoms (*Table 1*), the commonest being heartburn in 17 cases, distension in 12, and flatulence in 11. However, these symptoms were often volunteered only on direct questioning, and they accounted for most of the patients in the Visick II category. It was also noted that many of the symptoms had been present pre-operatively. For example, 15 of the 17 patients with heartburn had experienced this prior to surgery.

The problems of dumping and diarrhoea that form a major part of the morbidity after truncal vagotomy do not appear to be a problem after AGM + PTV. However, dumping after AGM + PTV has recently been described[13]. In our series, one patient described the features of dumping but these were controlled by dietary modification. Similarly, two patients complained of diarrhoea. They both described frequent loose stools up to six times a day, but not the explosive 'post-vagotomy diarrhoea' that is often described[14].

In Group B the known ulcer recurrence rate is 3 per cent. However, it is possible that some patients have moved away or were referred elsewhere when they developed symptoms of recurrence. Also the later patients in this group are within only 2 years of surgery and one would expect the cumulative ulcer recurrence rate to rise. These factors notwithstanding, the low recurrent ulcer rate in this group may well reflect a learning curve in mastery of the operation. Eight patients in Group B underwent cholecystectomy at the same time as AGM + PTV and a further four have undergone AGM + PTV with Nissen fundoplication. These additional procedures did not appear to affect the postoperative course or the long-term complications.

In summary we conclude that the operation of AGM + PTV is safe, not technically complex and acceptably rapid. The incidence of post-surgery symptoms is low and there is an acceptable ulcer recurrence rate at 5 years.

Acknowledgements

We wish to thank Mr D A D. Macleod for allowing us to include his patients in our study and Mrs Elizabeth Lumsden for her help with the word processor.

References

1. Taylor TV. Parietal cell vagotomy: longterm follow-up studies *Br J Surg* 1987; **74**. 971–2.
2. Hoffman J, Olesen A, Jensen HE. Prospective 14 to 18 year follow up study after parietal cell vagotomy *Br J Surg* 1987; **74**. 1056–9
3. Taylor TV, Gunn AA, Macleod DAD, Maclennan I. Anterior lesser curve seromyotomy and posterior truncal vagotomy in the treatment of chronic duodenal ulcer. *Lancet* 1982; **ii**: 346–8
4. Taylor TV. *A Colour Atlas of Seromyotomy for Chronic Duodenal Ulcer*. Wolfe single surgical procedures. London, 1984.
5. Taylor TV, Gunn AA, Macleod DAD *et al* Mortality and morbidity after anterior lesser curve seromyotomy with posterior truncal vagotomy for duodenal ulcer. *Br J Surg* 1985; **72**: 950–1.
6. Oostvogel HJM, Van Vroonhoven TJMV. Anterior lesser curve seromyotomy with posterior truncal vagotomy versus proximal gastric vagotomy. *Br J Surg* 1988; **75**: 121–4.
7. Moss JG, Gunn AA, Macleod DAD Anterior lesser curve seromyotomy and posterior truncal vagotomy for chronic duodenal ulcer. *J R Coll Surg Edinb* 1985; **30**: 239–40.
8. Goligher JC, Pulvertaft CN, Irvin TT *et al*. Five to eight year results of truncal vagotomy and pyloroplasty for duodenal ulcer *Br Med J* 1972; **i**· 7–13
9. Taylor TV Experience with the Lunderqvist Owman dilator in the upper gastro-intestinal tract. *Br J Surg* 1983; **70**. 445.
10. Johnston D Modern surgical attitudes to peptic ulceration. In: Hadfield J, Hobsley M, eds. *Current Surgical Practice* Vol. 1. London: Arnold, 1976: 89.
11. Goligher JC, Hill G, Kenny T, Nutter E. Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5–8 years. *Br J Surg* 1978; **65**. 145–51.
12. Stael von Holstein C, Graffner H, Oscarson J. One hundred patients ten years after parietal cell vagotomy *Br J Surg* 1987; **74**· 101–3
13. Barclay GR, Finlayson NDC, Taylor TV. Dumping syndrome following anterior lesser curve seromyotomy with posterior truncal vagotomy. *Br J Surg* 1987; **74**: 285.
14. Cuschieri A. Surgical management of severe intractable postvagotomy diarrhoea. *Br J Surg* 1986; **73**: 981–4.

Paper accepted 11 May 1988

Br. J. Surg. 1988, Vol. 75, September, 869–872

Highly selective vagotomy: a 14-year experience

D. J. Byrne, B. M. Brock, A. G. Morgan and W. A. F. McAdam

Airedale General Hospital, Keighley, West Yorkshire, UK

Correspondence to:
Mr W. A. F. McAdam, Airedale General Hospital, Steeton, Keighley, West Yorkshire BD20 6TD, UK

Since August 1971, 244 highly selective vagotomies were performed for pyloric and duodenal ulceration by one surgeon (W.A.F.M.). There was one postoperative death. Twenty (8 per cent) patients were lost to follow-up. The remaining 223 patients were followed up for 1 to 14 years (mean 4·2 years). On the modified Visick grading system 83·4 per cent were Visick I or II and 16·6 per cent were Visick III or IV. The failures were mainly recurrences. The recurrence rate was 11·2 per cent. Certain factors were examined to try to elucidate those influencing recurrence rate but no significant prognostic indicator was found. Acid studies were analysed and no significant relationship between these and the development of a recurrence could be found. The second 100 vagotomies were better than the first as judged by the results of studies of insulin-stimulated acid. Finally, we question whether all recurrences should automatically be regarded as treatment failures and the patients classified as Visick IV.

Keywords: Highly selective vagotomy, duodenal ulcer

Many authors regard highly selective vagotomy (HSV) as the operation of choice for the elective treatment of duodenal ulceration[1–7]. Since the first reports of HSV[8,9] there have been many emphasizing its safety and low incidence of associated side-effects. However, the recurrent ulcer rate has been worrying; in some series it has been greater than 25 per cent[10,11]; conversely, Romeo *et al.*[12] reported a recurrence rate of 1 per cent. The present study was undertaken to review the results of 244 HSVs performed by one surgeon at a district general hospital. We looked for any factors that might predict which patients would get recurrent ulcers and then studied the management of the recurrences in an attempt to assess the trouble caused to the patient by the recurrence.

Patients and methods

From August 1971 to September 1985, 244 HSVs were performed for patients with prepyloric (3), pyloric channel (1) and duodenal (240) ulceration. Of these patients, 188 were men and 56 were women. Their ages ranged from 18 to 78 years with a mean of 42 years. The main symptom for which surgery was performed was pain (240 patients). Other indications were recurrent bleeding from the ulcer (8 patients), and previous perforation (2). The average duration of symptoms was 12·8 years (range 1–50 years).

Some points in our operative technique differ from the standard[9]. Instead of a second assistant a 'mechanical assistant' is used to retract the liver[13]. The vessels and nerves are tied using a continuous-feed ligature carrier based on models described previously[14–16]; this shortens the operating time The lesser curve is always covered by approximating the anterior and posterior peritonealized surfaces of the stomach over the bare area produced by the operation, to eliminate the risk of lesser curve necrosis. Finally, the whole operation is performed from the anterior aspect of the stomach, there being no need to turn the stomach over to deal with the posterior leaf of the lesser omentum

Basal acid output (BAO) and peak acid output with pentagastrin stimulation (PAOpg, 0·6 μg pentagastrin/kg) were measured in patients pre-operatively and BAO and PAOpg as well as insulin-stimulated acid studies were performed on patients 2 weeks postoperatively and in the first half of the series at 1 year postoperatively as well. In performing the insulin test a nasogastric tube was passed after an overnight fast. Basal acid output was recorded in four consecutive 15-minute samples Eight consecutive 15-minute samples were collected after giving 0·2 units/kg soluble insulin In this procedure the first two collections after the insulin dose are ignored and collections 3, 4, 5, 6, 7 and 8 are examined. If collections 3 or 4 are positive then the result is regarded as an early positive; if 5, 6, 7 or 8 is positive then it is regarded as late positive. A positive response is one in which there is an increase in titrable acid concentration of at least 20 mmol/l after insulin (collections 3–8) compared with the average of the two highest 15-minute basal collections These results were compared statistically using Wilcoxon's two-sample test and the χ^2 test.

Follow-up took place at a special gastric clinic using a standard questionnaire completed by two of the authors (W A F M., A G.M.) Each patient was seen 3 months, 6 months and 1 year postoperatively and yearly thereafter Recurrent symptoms were investigated by upper gastrointestinal endoscopy. Asymptomatic patients were not subjected to endoscopy.

Results

There was one postoperative death (acute gastric dilatation). Immediate postoperative complications occurred in 49 (20 per cent) patients and are detailed in *Table 1*. The follow-up ranged from 1 to 14 years (mean 4·2 years). Of the 244 patients, one died (myocardial infarction), 20 (8·2 per cent) were lost to follow-up within a year of their surgery (mostly because they moved away from the area) and of the remaining 223, 147 (65·9 per cent) were classified on the modified Visick grading system[17] as Visick I, 39 (17·5 per cent) were Visick II, 9 (4·0 per cent) were Visick III and 28 (12·6 per cent) were Visick IV. The reasons for the poor results (i.e. Visick III and IV) are

Table 1 *Immediate postoperative complications in 49 patients after highly selective vagotomy*

Complication	No of patients
Chest infection*	26
Wound infection	9
Wound haematoma	9
Deep vein thrombosis†	2
Burst abdomen	2
Vomiting	1
Omental vessel bleed‡	1
Left ventricular failure	1
Sub-phrenic abscess‡	1
Bleed from large gastric ulcer on lesser curve (partial thickness lesser curve necrosis)	1

* Clinical impression supported by chest X-ray and sputum cultures, † one clinically diagnosed; the other confirmed by venography; ‡ required reoperation

0007–1323/88/090869–04$3 00

Table 2 *Factors causing poor outcome after highly selective vagotomy*

Visick grading	Reasons for grading	No. of patients
III	Pain with negative endoscopy	4
	Diarrhoea	2
	Fullness	1
	Vomiting	1
	Persistent dysphagia (>1 year)	1
IV	Recurrence	25
	Nausea/vomiting	1
	Gastric stasis (requiring gastroenterostomy)	1
	Fullness	1

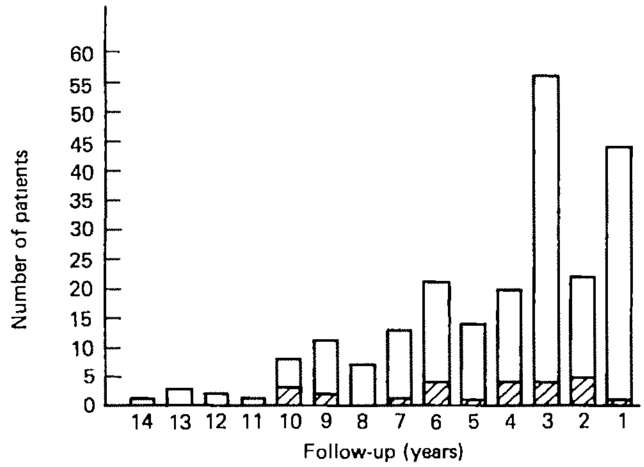


Figure 1 *Distribution of operations* ☐ *and recurrent ulcers* ▨ *with time*

shown in *Table 2*. There were only two cases of dumping but both were so mild that the patients were classified as Visick II. Two other patients had prolonged mild postoperative diarrhoea. These patients were easily controlled with medication and were classified as Visick III.

We had 25 patients with endoscopy-diagnosed recurrence. There were 20 men and the patients' ages ranged from 22 to 66 years (mean 43 years). The recurrences occurred up to 10 years after operation and the distribution of the recurrences in time is shown in *Figure 1*.

Pre-operatively, BAO and PAOpg were measured in 219 patients. Postoperative BAO and PAOpg studies were performed 2 weeks after operation in 215 patients and 1 year after operation in 111 patients. Studies of insulin-stimulated acid were performed 2 weeks postoperatively in 197 patients and 1 year postoperatively in 100 patients. The results of the acid studies can be seen in *Table 3*. The 2-week and 1-year postoperative insulin tests were compared in 88 patients: in 38 (43·2 per cent) there was a drop in grade as defined by Hollander[18] and Ross and Kay[19] (i.e. change from negative to late or early positive (28 patients) or late positive to early positive (10 patients)); this is in close agreement with a previous report[20]. The studies of acid in duodenal ulcer patients with and without recurrences were compared (*Table 4*) and this showed no statistical difference between the two groups.

Management of the 25 patients with recurrent ulceration is shown in *Table 5*.

Discussion

First, it is important to note that acid secretory status varies with age, weight, sex and blood group. To include all these parameters in a calculation of a 'standard acid secretion' is not possible in everyday clinical work and we, therefore, have not used them. We found that patients with recurrent ulcers had slightly higher pre-operative BAO and PAOpg, 2-week postoperative BAO and 1-year postoperative BAO and PAOpg, and a slightly lower negative insulin test response rate (*Table 4*). It is interesting to note that 50 per cent of the patients with recurrent ulcers had a negative insulin response 2 weeks after operation and more than 10 per cent of non-recurrent patients had early positive insulin tests. Of those patients who had no recurrence and who had an insulin test performed at 2 weeks and 1 year postoperatively, 43 per cent showed a deterioration of their insulin test results with time; recurrent patients had a similar incidence of deterioration (42 per cent). This has been

Table 3 *Results of acid studies and insulin tests*

Studies	*n*	BAO (mmol/h)*	PAOpg (mmol/h)*
Acid output			
Pre-operative	219	5·4 (0·2–30·6)	54·0 (7·5–97·2)
2 weeks post-op.	215	0·5 (0–14·5)	25·3 (6·0–55·2)
1 year post-op.	111	1·7 (0–13·5)	26·9 (4·8–65·1)

	n	Negative†	Late positive†	Early positive†
Insulin tests				
2 weeks post-op	197	134 (68)	42 (21·3)	21 (10·7)
1 year post-op.	100	53 (53)	26 (26)	21 (21)

BAO, basal acid output. PAOpg, peak acid output with pentagastrin stimulation; * median (range in parentheses), † number of patients (percentage in parentheses)

Table 4 *Comparison of acid studies recurrence/non-recurrence*

Studies	Ulcer recurrence	*n*	BAO (mmol/h)*	PAOpg (mmol/h)*
Acid output	Pre-operative			
	Non-recurrent	197	7·5 (0·4–30·6)	51·4 (7·5–73·4)
	Recurrent	22	8·7 (0·2–23·1)	57·0 (19·8–97·2)
	2 weeks post-op.			
	Non-recurrent	193	0·9 (0–12·2)	24·6 (8·2–38·1)
	Recurrent	22	1·4 (0–14·5)	24·0 (6·0–55·2)
	1 year post-op.			
	Non-recurrent	96	1·4 (0–10·5)	21·3 (4·8–65·1)
	Recurrent	15	2·1 (0·08–13·5)	26·4 (7·8–54·6)

			Negative†	Late positive†	Early positive†
Insulin tests	2 weeks post-op				
	Non-recurrent	177	121 (68·4)	36 (20·3)	20 (11·3)
	Recurrent	20	10 (50)	5 (25)	5 (25)

* Median (range in parentheses); † number of patients (percentage in parentheses)

Table 5 *Management of recurrent ulceration*

Treatment	Surgery (partial gastrectomy)	Medical: short-term (<6 months)	Medical: long-term (>6 months)
No. of patients	3	12	10
Follow-up (years)	1, 2 and 6	1–11 (mean 4)	1–6 (mean 3)
Comments	No further recurrence	No further recurrence	Maintenance medical treatment required by all patients in order to remain symptom-free

observed previously[7,21,22]. These acid test comparisons between patients with recurrent and non-recurrent ulcers show no statistical difference at the 5 per cent level in this series. Other calculations, based on acid studies and quoted in the literature as being of value in predicting recurrent ulcer formation, were not helpful in this group of patients[23,24].

Although the insulin test does not help in the prediction of ulcer recurrence in an individual we feel that it is important to use it as a form of 'vagotomy quality control'. Without it we believe no HSV should be done. Markey *et al.*[25] state that the main use of acid studies is for quality control, although they go on to say that the Burge test[26] is probably a better form of quality control, because remedial measures can be taken at the time if a positive result is found. However, the insulin test does provide the surgeon with a feedback on his vagotomy technique. In this context we were surprised to find that this one surgeon's insulin test results for the second hundred operations were better than those of the first hundred. This casts doubt on the idea that the learning curve flattens out after, say, 20 operations and it should be possible for others to confirm or refute this finding.

All patients with recurrence were initially managed by medication. Those with no response were then treated surgically. In those patients who responded to medication a period without any treatment was tried after an interval of 6 weeks to 6 months. If the symptoms recurred on stopping treatment then the medical regimen was reinstituted. It has been shown previously that the recurrence rate for prepyloric ulcers is greater than that for duodenal ulcers[3,27] but the numbers in this series were too small for comparison. There was no age difference between those patients with and without recurrences. This has been observed previously[28–30]. The duration of symptoms was on average 2 years longer for patients without recurrence than for those with recurrence and the recurrence rate was slightly higher for men than for women. Patients with recurrence smoked more cigarettes than those without but this was not statistically significant. Blood groups were broadly similar in the recurrent and non-recurrent groups although there were more A Rh-ve patients in the recurrent ulcer group (14·3 per cent *versus* 3·9 per cent, difference not significant). However, none of this information is useful in predicting a recurrence in a particular patient.

The recurrence rate certainly did not appear to decrease with time (*Figure 1*). Other authors[6,7] who have reported a 10-year follow-up have made the same observation. At the time of writing there have been no recurrences after 10 years, but we agree with Hollinshead *et al.*[3] that follow-up for a long period (perhaps 20 years) is necessary to assess the true status of this or any other operation for peptic ulcer disease.

Only three of our patients with recurrence required further surgery. Most of the others were easily managed medically. This ease of management of the majority of the recurrences after HSV has been noted before[28] and calls into question the routine classification of all recurrences as Visick grade IV, as has been done previously[4,31]. It also challenges Jordan's[32] statement that all HSV recurrences should be treated by gastric resection. Of 25 patients with recurrence, 12 were asymptomatic and on no medication within 6 months of the recurrence being diagnosed and these patients had no further trouble during the subsequent follow-up period of 1–11 years (mean 4 years). It is also interesting to note that four of the above twelve patients (who were resistant to medical treatment of their ulcer before HSV) responded to a single course of H_2 blockers postoperatively. HSV certainly modifies disease and even in those patients with recurrence, the attacks were less frequent and less severe than previously. Moreover, despite the recurrence of the ulcer all these patients were satisfied with the results of surgery.

In conclusion, the authors still feel that HSV is the best operation for the elective surgical treatment of duodenal ulceration. Even if it does prove to have a higher recurrence rate than other operations for duodenal ulceration, it has a significantly lower incidence of the undesirable side-effects seen after more radical gastric surgical procedures. We agree with other authors[33,34] who state that, because HSV modifies the disease process, treatment of recurrence is easier than treating complications of more radical operations, such as dumping. Finally, we would stress that the true recurrence rate can only be assessed at least 10 years postoperatively.

References

1. Johnston D. Peptic ulceration. highly selective vagotomy In: Keen G, ed *Operative Surgery and Management*. Bristol· Wright, 1981: 69.
2. De Miguel J. Late results of proximal gastric vagotomy without drainage for duodenal ulcer· 5–9-year follow-up. *Br J Surg* 1982; **69**: 7–10.
3. Hollinshead JW, Smith RC, Gillett DJ. Parietal cell vagotomy experience with 114 patients with prepyloric or duodenal ulcer. *World J Surg* 1982; **6**: 596–602.
4. Stoddard CJ, Johnson AG, Duthie HL The four to eight year results of the Sheffield trial of elective duodenal ulcer surgery—highly selective or truncal vagotomy? *Br J Surg* 1984; **71**· 779–82.
5. Enskog L, Rydberg B, Adami HO, Enander LK, Ingvar C. Clinical results 1–10 years after highly selective vagotomy in 306 patients with prepyloric and duodenal ulcer disease *Br J Surg* 1986, **73**: 357–60.
6. Rossi RL, Dial PF, Georgi B, Braasch JW, Shea JA A five to ten year follow-up study of parietal cell vagotomy *Surg Gynecol Obstet* 1986; **162**: 301–6
7 Van Holstein C, Graffner H, Oscarson J. One hundred patients ten years after parietal cell vagotomy. *Br J Surg* 1987; **74**· 101–3.
8. Amdrup E, Jensen HE Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum: a preliminary report of results in patients with duodenal ulcer. *Gastroenterology* 1970, **59**. 522–7.
9. Johnson D, Wilkinson AR. Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. *Br J Surg* 1970; **57**: 289–96.
10. Madsen P, Kronborg O. Recurrent ulcer 5½–8 years after highly selective vagotomy without drainage and selective vagotomy with pyloroplasty. *Scand J Gastroenterol* 1980, **15** 193–9.
11. Hoffmann J, Jensen HE, Schulze S, Poulsen PE, Christiansen J. Prospective controlled vagotomy trial for duodenal ulcer: results after 5 years. *Br J Surg* 1984; **71**· 582–5.
12. Romeo G, Giovinetto A, Sanfilippo G, Cali R, Catania G, Basile F. Follow-up study in 402 patients after parietal cell vagotomy for duodenal ulcer. *Int Surg* 1981; **66**: 303–6.
13. Tinckler L. Mechanical assistance in operative surgery. *On Call* 1974; **8**: 12–13.
14. Tibbs DJ. A continuous-feed aneurysm needle. *Br Med J* 1952; **2**: 1201.
15. Dowling BL. Fine continuous-feed aneurysm needle *Br Med J* 1970; **2**: 677.
16. Tinckler L. A universal ligature applicator *Med J Aust* 1971; **2**: 961–2.
17. Goligher JC, Pulvertaft CN, de Dombal FT *et al* Five- to eight-year results of Leeds/York controlled trial of elective surgery for duodenal ulcer. *Br Med J* 1968; **2**: 781–7.
18. Hollander F Laboratory procedures in the study of vagotomy with particular reference to the insulin test *Gastroenterology* 1948, **11**: 419–25.
19. Ross B, Kay AW. The insulin test after vagotomy. *Gastroenterology* 1964; **46**: 379–86.
20 Smith IS, Gillespie G, Elder JB, Gillespie IE, Kay AW Time of conversion of insulin response after vagotomy *Gastroenterology* 1972; **62**: 912–7
21. Hedenstedt S, Lundquist G, Moberg S Selective proximal vagotomy (SPV) in the treatment of duodenal ulcer *Acta Chir Scand* 1972; **138**: 591–6.
22 Solhaug JH, Bjerkeset T, Holvorsen JF Highly selective vagotomy in the treatment of duodenal ulcer in a teaching hospital. *Surgery* 1977; **82**: 248–53.
23. Graffner H, Liedberg G, Oscarson J Acid secretory tests in peptic ulcer disease before and after parietal cell vagotomy *Scand J Gastroenterol* 1984; **21**. 41–6.
24. Ornsholt J, Jorgensen HS, Marqversen J Recovery of gastric acid after vagotomy with and without drainage *Eur Surg Res* 1982, **14**: 56–64.

25. Markey DA, Tovey FI, Heald RJ. Results of proximal gastric vagotomy over 1–5 years in a district general hospital. *Br J Surg* 1979; **66**: 39–42.
26. Burge H, Vane JR. Method of testing for complete nerve section during vagotomy. *Br Med J* 1958; **1**: 615–8
27. Andersen D, Hostrup H, Amdrup E. The Aarhus County vagotomy trial. II. An interim report on reduction in acid secretion and ulcer recurrence rate following parietal cell vagotomy and selective gastric vagotomy *World J Surg* 1978; **2**: 91–100.
28. Busman DC, Munting JDK. Results of highly selective vagotomy in a non-university teaching hospital. *Br J Surg* 1982; **69**. 620–4.
29. Lunde O, Liavay I, Roland M. Recurrent ulceration after proximal gastric vagotomy for duodenal ulcer. *World J Surg* 1983; **7**. 751–6.
30. Jensen HE, Kjaergaard J, Meisner S. Ulcer recurrence two to twelve years after parietal cell vagotomy for duodenal ulcer. *Surgery* 1983; **94**: 802–6.
31. Christiansen J, Jensen HE, Ejby-Poulsen P, Bardram L, Henriksen FW. Prospective controlled vagotomy trial for duodenal ulcer. *Ann Surg* 1981; **193**: 49–55.
32. Jordan GL Jr. Recurrence after highly selective vagotomy should be treated by gastric resection *Am J Surg* 1986; **152**: 312–3.
33. Gleysteen JJ, Condon RE, Tapper EJ. Prospective trial of proximal gastric vagotomy. *Surgery* 1983, **94**: 15–20.
34. Steger AC, Galland RB, Spencer J. Remaining indications for vagotomy with drainage or antrectomy in duodenal ulcer. *Ann R Coll Surg Engl* 1986; **68**: 24–6.

Paper accepted 12 May 1988

Why more and more Surgeons are selecting Coated VICRYL*.

Coated VICRYL*
(polyglactin 910) braided sutures

ETHICON
a Johnson & Johnson company

ETHICON Ltd., P.O. Box 408, Bankhead Avenue,
Edinburgh EH11 4HE, United Kingdom.
*Trademark © ETHICON Ltd 1988.

TECHNICAL DATA

COATED VICRYL* (POLYGLACTIN 910) STERILISED BRAIDED SYNTHETIC ABSORBABLE SUTURE

Presentation The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category.
Not applicable.

Package Quantities Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 packs contained in a film wrapped drawer style carton.

Further Information No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No 0508/0009
Br. Pat. No. 1583390

Date of Preparation of Data Sheet April 1981.
Revised 11/1987.

ETHICON LTD.
PO BOX 408, BANKHEAD AVE
EDINBURGH EH11 4HE

---

*Trademark

Br. J. Surg. 1988, Vol. 75, September, 873–874

Hyperparathyroidism after neck irradiation

T. J. Christmas,
C. R. Chapple,
J. G. Noble,
E. J. G. Milroy and
A. G. A. Cowie

Department of Urology, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Correspondence to:
Mr T. J. Christmas

A retrospective review of 1550 cases of hyperparathyroidism (HPT) treated surgically over a 30-year period reveals a past history of exposure to neck irradiation in 10 cases (0·7 per cent). The indication for radiotherapy was benign disease in nine and papillary thyroid carcinoma in one case. The mean interval between radiation exposure and the detection of HPT was 32 years (range 3–63 years). Patients treated with radioactive iodine alone developed HPT after a mean of 5 years while the interval for those treated with external beam therapy alone was a mean of 44 years. The parathyroid histology was adenoma in six cases, carcinoma in three cases and nodular hyperplasia in one case. All patients had coincident benign thyroid disease apart from one that had previously had papillary carcinoma and another with follicular carcinoma. Neck irradiation has been shown to confer an increased risk of HPT due to parathyroid adenoma and carcinoma. Radiotherapy for benign disease has generally been abandoned and these cases demonstrate a further contra-indication for the use of neck irradiation.

Keywords: Hyperparathyroidism, neck irradiation, radioactive iodine therapy, parathyroid carcinoma

Neoplasia following external irradiation was first described in workers with luminous paint who developed osteogenic sarcomata[1]. A large number of patients underwent head and neck external beam irradiation between 1900 and 1950 for benign conditions such as acne, tonsillitis, tuberculosis, hirsutism, thymus enlargement and skin lesions[2]. This practice was commoner in the USA and continental Europe. An increase in the incidence of neoplastic diseases of thyroid, salivary glands, skin and parathyroids has been described in these patients[3–6]. Similarly, the exposure of experimental animals to irradiation may lead to neoplastic disease. In rats, parathyroid hyperplasia, adenomas and carcinomas have been found after administration of radiation in the form of external beam or radioactive iodine treatment[7,8].

Patients and methods

The records of 1550 consecutive patients with HPT treated surgically at The Middlesex and University College Hospitals from 1959 onward were reviewed retrospectively for a past history of neck irradiation, radioiodine therapy or coexistent thyroid disease. A total of 10 patients (0·7 per cent) were found with a definite history of therapeutic irradiation. Of these, five had undergone external beam radiotherapy alone, two had received both external beam radiotherapy and radioactive iodine treatment, two had received radioactive iodine treatment alone and one had local radium wire implants. Of these patients, nine were female and one was male.

Results

The mean age at which the seven patients had been treated with external beam therapy was 18 years (range 1–37 years) and the indications for its use were tuberculous cervical lymphadenitis in two, hyperthyroidism in two, goitre in one, papillary carcinoma of the thyroid in one and a benign skin lesion in one case (*Table 1*). The dose of radiation used was not known in all cases but the range was 300–800 rad. Radioactive iodine was given to four patients at a mean age of 48 years (range 25–62 years) and the indications for its use were hyperthyroidism in three cases and papillary carcinoma of the thyroid in one case. Radium wire implants were inserted into the neck of one patient at the age of 18 years as treatment for tuberculous cervical lymphadenitis.

The total mean period between radiation exposure and the development of HPT was 32 years (range 3–63 years). However, the interval between external beam therapy alone and HPT was a mean of 44 years (range 25–63 years), whereas HPT followed radioactive iodine therapy in a mean of 5 years (range 3–9 years).

The patient who had been treated with radium wire implants developed HPT 48 years later.

All patients were hypercalcaemic at presentation and those that had parathyroid hormone assay had levels above 160 pg/ml. Neck exploration was performed in all cases and apart from the patient who had previously undergone total thyroidectomy for papillary carcinoma, all had macroscopically abnormal thyroid glands.

Histological examination of the parathyroids showed a single adenoma in six cases, carcinoma in three cases and nodular hyperplasia in one case. Thyroid histology revealed multinodular goitre in four cases, fibrosis and lymphocytic infiltrate in one, a cyst in one and follicular carcinoma in one case (patient with parathyroid carcinoma). The patients with parathyroid carcinoma had previously undergone external beam radiotherapy, 25, 49 and 53 years earlier. Multiple tumours occurred within the irradiated area in three cases. In one individual, six basal cell carcinomas and two squamous cell carcinomas developed in the irradiated cervical skin, a breast carcinoma appeared in the irradiated upper inner quadrant of the breast and a parathyroid adenoma formed in a lower gland. These tumours did not begin to appear until 42 years after irradiation. One patient developed follicular carcinoma of the thyroid and carcinoma of the parathyroid synchronously 25 years after external beam therapy for cervical tuberculosis. He ultimately died of metastatic parathyroid carcinoma. A third patient underwent thyroid lobectomy for an adenoma 16 years after external beam therapy and formed a parathyroid adenoma another 16 years later.

Discussion

The first reported effect of irradiation on parathyroid glands was hypoparathyroidism after radioactive iodine therapy in thyrotoxic patients, and this was thought to be due to direct radiation tissue destruction[9,10]. In 1975 Rosen *et al.* reported

---

This paper was presented at the British Association of Endocrine Surgeons' Annual Meeting in Cardiff 1988

Table 1 *Details of 10 patients developing hyperparathyroidism after neck irradiation*

Age at diagnosis of hyperparathyroidism (years)	Form of radiotherapy	Time interval (years)	Parathyroid histology	Thyroid histology	Other tumours
65	^{131}I	3	Adenoma	Cyst +fibrosis	
61	^{131}I	4	Adenoma	Fibrosis	
64	EBRT	63	Adenoma	Fibrosis +lymphocytes	BCC ×6, SCC ×2, Carcinoma of breast
37	^{131}I+EBRT	?	Adenoma	Fibrosis	
34	EBRT	32	Adenoma	Colloid goitre	Thyroid adenoma
34	^{131}I+EBRT	9	Adenoma	Previous papillary carcinoma	
66	Radium wire implants	48	Nodular hyperplasia	Colloid goitre	
62	EBRT	25	Carcinoma	Follicular carcinoma	
67	EBRT	49	Carcinoma	Colloid goitre	
79	EBRT	53	Carcinoma	Colloid goitre	

EBRT, external beam radiotherapy; ^{131}I, radioactive iodine therapy; BCC, basal cell carcinoma; SCC, squamous cell carcinoma

the first case of HPT following neck irradiation in man[11]. In 1977 Triggs and Williams showed that the administration of low doses of radioactive iodine to newborn rats induced the formation of parathyroid adenomas in 61 per cent at 15 months and there was associated hypercalcaemia in some cases[8]. The patients in our series were similarly found to develop HPT relatively soon after radioactive iodine therapy (mean 5 years). However, it should be noted that in most cases rat parathyroid glands lie within the substance of the thyroid and one would therefore expect them to be exposed to a higher level of radiation than human parathyroids during radioactive iodine therapy.

Tisell *et al.* followed up 100 patients treated with X-rays for tuberculous adenitis of the neck between 1930 and 1946: in 1977, 11 of these patients were found to have HPT, attributable to adenomas in 7 and hyperplasia in 4[12]. All 11 patients had coexistent thyroid disease and 2 had papillary carcinoma. Interestingly, 36 per cent of these patients did not realize, or had forgotten, that they had received X-ray treatment. This factor and the less liberal use of X-ray therapy for benign conditions in this country may account for the less frequent history of irradiation in our series of HPT patients. A series of 400 HPT patients from Detroit, USA, where 3 per cent of age-matched controls had a previous history of neck irradiation, showed a 17 per cent prevalence of previous neck irradiation and a mean latency of 36 years[2].

The occurrence of parathyroid carcinoma after neck irradiation has been described in only two previous cases[12,13]. Out of a series of 678 cases of surgically treated HPT 20 (2·9 per cent) had parathyroid carcinoma[14]. The three cases of carcinoma (30 per cent) in our series demonstrate a statistically significant increase ($P < 0{\cdot}01$) in the incidence of parathyroid carcinoma in patients with HPT who have previously received neck irradiation. The reason why this association has been noticed on only two previous occasions may be because of the long latency period (mean 43 years) and the sometimes difficult histological diagnosis.

These late sequelae represent yet another contra-indication for the use of radiotherapy in the treatment of benign conditions of the head and neck. Although this practice has now largely been abandoned, further cases of neoplastic parathyroid disease should be anticipated over the next 20 years. A more conservative approach should perhaps also be adopted to the use of radioactive iodine in thyrotoxic patients in the light of the above findings.

References

1. Martland HS Occupational poisoning in manufacture of luminous watch dials *JAMA* 1929; **92**: 466
2. Rao SD, Frame B, Miller MJ, Kleerekoper M, Block MA, Parfitt M. Hyperparathyroidism following head and neck irradiation. *Arch Intern Med* 1980; **140**: 205–7.
3. Favus MJ, Schneider AB, Stachura ME *et al.* Thyroid cancer occurring as a late consequence of head and neck irradiation: evaluation of 1056 patients. *N Engl J Med* 1976; **294**: 1019–25.
4. Schneider AB, Favus MJ, Stachura ME *et al.* Salivary gland neoplasms as a late consequence of head and neck irradiation. *Ann Intern Med* 1977, **87**: 160–4.
5. Modan B, Baidatz D, Mart H *et al.* Radiation-induced head and neck tumours *Lancet* 1974; i· 277–9.
6. Tisell LE, Carlsson S, Lindberg S *et al.* Autonomous hyperparathyroidism: a possible late complication of neck radiotherapy. *Acta Chir Scand* 1976; **142**: 367–73.
7. Potter GD, Lindsay S, Chaikoff IL Induction of neoplasms in rat thyroid glands by low doses of radioiodine. *Arch Pathol* 1960; **69**: 257–69.
8. Triggs SM, Williams ED. Irradiation of the thyroid as a cause of parathyroid adenoma. *Lancet* 1977; **i**. 593–4.
9. Tighe WJ. Temporary hypoparathyroidism following radioactive iodine treatment for thyrotoxicosis. *J Clin Endocrinol* 1952; **12**: 1220
10. Eipe J, Johnson SA, Klamko RT, Bronsky D. Hypoparathyroidism following I^{131} therapy for hyperthyroidism *Arch Intern Med* 1968; **121**: 270–2.
11. Rosen IB, Strawbridge HG, Bain J A case of hyperparathyroidism associated with radiation to the head and neck area. *Cancer* 1975; **36**· 1111.
12. Tisell LE, Hansson G, Lindberg S, Ragnhult I. Hyperparathyroidism in persons treated with x-rays for tuberculous cervical adenitis. *Cancer* 1977; **40**: 846–54.
13. Ireland JP, Fleming SJ, Levison DA, Cattell WR, Baker LRI Parathyroid carcinoma associated with chronic renal failure and previous radiotherapy to the neck. *J Clin Pathol* 1985; **38**: 1114–8.
14. Smith JF, Coombs RRH. Histological diagnosis of carcinoma of the parathyroid gland. *J Clin Pathol* 1984; **37**: 1370–8

Paper accepted 12 May 1988

Br. J. Surg. 1988, Vol. 75, September,
875–878

Resting energy expenditure in the critically ill: estimations versus measurement

A prospective trial was conducted in 20 surgical intensive care unit patients receiving mechanical ventilation to compare estimates of resting energy expenditure (REE) with the measured values. The 12 women and 8 men (mean age 61·7 ± 2·8 (s.e.m.) years) underwent a full nutritional assessment before measurement of their REE by indirect calorimetry using the MGM II metabolic cart (Utah Medical). Their REE was estimated by the Harris–Benedict formula (mean 1324 ± 53 (s.e.m.) kcal/day) as well as an empirical formula (where empirical formula = 22 × body weight in kg) (1370 ± 68 (s.e.m.) kcal/day). Results by either estimate were not statistically different from the measured resting energy expenditure (MREE) (1382 ± 130 (s.e.m.) kcal/day), by one-way analysis of variance. No multiplication factors were needed to relate the Harris–Benedict formula to MREE in this critically ill population and the estimate by the empirical formula was as good and simpler to perform. Although values by the Harris–Benedict formula and empirical formula correlated significantly with MREE ($P < 0.05$) *the correlation coefficients were low: 0·48 and 0·45 respectively. Thus, mean estimates were excellent for the group but less predictive for the individual. Multiple linear regressions did reveal that body composition and metabolic stress were of greater predictive value, since an equation relating weight* ($P < 0.003$), *sex* ($P < 0.003$), *white blood cell count* ($P < 0.003$) *and 24-h urinary creatinine excretion* ($P < 0.05$) *could predict 76 per cent of the variation* ($r = 0.87$) *in the MREE with an overall significance of* $P = 0.0002$. *Given the importance of matching energy intake to needs in many critically ill patients who are mechanically ventilated, accurate measurement of the REE is recommended now that instrumentation is equal to the task.*

Keywords: Resting energy expenditure, indirect calorimetry

D. C. Hunter, T. Jaksic, D. Lewis, P. N. Benotti, G. L. Blackburn and B. R. Bistrian

The Laboratory of Nutrition and Infection, Cancer Research Institute, New England Deaconess Hospital, Harvard Medical School, 194 Pilgrim Rd, Boston, Massachusetts 02215, USA

Correspondence to:
Dr B. R. Bistrian

The consequences of overfeeding, which leads to hepatic lipogenesis and an increase in oxygen consumption and carbon dioxide production, as well as other detrimental consequences, has been well documented. This is of particular relevance to the ventilated patient who, if overfed, may present weaning difficulties[1].

The recognition of the importance of providing patients with the correct caloric intake is well illustrated by the number of equations and formulae that have been developed to estimate the resting energy expenditure which should satisfy 75–100 per cent of a hospitalized patient's energy requirements[2–5].

Now that easily transportable indirect calorimeters are available and reliable measurements of resting energy expenditure (REE) can be made[6], we decided to test the applicability of some commonly used formulae, in stressed, ventilated, surgical intensive care unit patients.

Patients and methods

Twenty surgical intensive care unit patients receiving mechanical ventilation by either the 7200 or MAI ventilator (Puritan Bennett, California, USA) were studied prospectively. Feeding, which was often limited by fluid restriction (for a variety of causes, e.g renal failure, gross cardiac failure, hepatorenal syndrome), was continued The age, weight, height and body temperature were recorded along with their clinical history. A 24-h collection of urine was obtained from each patient and the quantity of urea nitrogen and creatinine therein was measured. Also measured from the patient's serum were the albumin concentration and a complete blood count including the total white cell count and the number of banded forms Patients were then connected to the MGM II (Utah Medical, Utah, USA) indirect calorimeter and their oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were measured while patients were in a stable condition From these measurements a computer integral to the calorimeter calculated the REE using the following equation (Bursztein *et al.*[7]):

$$\mathrm{REE} = 5\ 083\dot{V}_{O_2} - 0\ 138\dot{V}_{CO_2} - 0{\cdot}128\mathrm{NM}$$

where REE is the resting energy expenditure in kcal/day, and NM is derived from the urine urea nitrogen in g/min

Commonly used estimations for REE were also calculated· the Harris–Benedict formula for males

$$\mathrm{REE} = 66 + (13{\cdot}8 \times W) + (5 \times H) - (6{\cdot}8 \times A) \qquad (1)$$

and for females:

$$\mathrm{REE} = 665 + (9{\cdot}6 \times W) + (1\ 8 \times H) - (4{\cdot}7 \times A)$$

(where W is the actual weight in kilograms, H is the height in centimetres, and A is the age in years), an empirical formula·

$$\mathrm{REE} = 10 \times \text{body weight in pounds} \qquad (2)$$

or

$$\mathrm{REE} = 22 \times \text{body weight in kg}$$

and an equation relating resting energy expenditure to urinary creatinine:

$$(0\ 488x) + 964 \qquad (3)$$

where x = mg urinary creatinine per 24 h.

Statistical analysis was completed using means, standard error of mean, one-way analysis of variance, stepwise linear regression analysis,

0007-1323/88/090875-04$3 00

Table 1 *Details of the 20 patients included in the study*

Patient no.	Diagnosis	Age (years)	Sex (M/F)	Height (cm)	Weight (kg)
1	Perforated diverticulitis; ARDS; Ca prostate	70	M	165	47
2	Obstructive jaundice	81	M	150	61
3	Liver transplant (cryptogenic cirrhosis)	56	M	180	93
4	Left pneumonectomy for aspergilloma, pneumonia, bronchopleural fistula	48	M	173	48
5	Pancreatic Ca, laparotomy, splenectomy	66	F	178	64
6	Liver transplant	58	F	163	57
7	Oesophagogastrectomy; colonic interposition	61	F	163	63
8	Repair abdominal aortic aneurysm, re-implantation renal arteries	64	F	158	61
9	Pelvic exenteration, ovarian Ca	56	F	160	69
10	Renal transplant, CMV pneumonitis	52	F	168	71
11	Crohn's disease, subtotal colectomy	61	F	160	44
12	Liver transplant	56	F	160	64
13	Whipple's operation for pancreatic Ca	80	F	188	80
14	Coronary artery bypass graft, aortic valve replacement	63	M	170	80
15	Coronary artery bypass graft	66	M	177	73
16	Liver transplant	24	F	170	67
17	Diabetes, heart failure, peripheral vascular disease, thalassaemia, right above-knee amputation	72	F	155	45
18	Coronary artery disease, peripheral vascular disease, ileofemoral and femoral–popliteal GORE-TEX® graft	70	F	142	42
19	Chronic heart failure, bronchiectasis, coronary artery bypass graft, pneumonia	77	F	160	42
20	Chronic active hepatitis, liver failure, renal failure, encephalopathy	57	F	160	70

ARDS, adult respiratory distress syndrome; Ca, cancer; CMV, cytomegalovirus. GORE-TEX® is a registered trademark of W. L. Gore Associates Inc.

Table 2 *Basic data from the 20 patients under study*

Patient no.	Temperature (°C)	Albumin (g/l)	WBC (1000/mm³)	Bands (% WBC)
1	37·8	22	6·4	18
2	37·8	21	12·9	3
3	37·8	14	2·3	45
4	37·2	18	52·3	27
5	37·8	19	15·4	31
6	37·6	28	11·1	32
7	38·3	21	16·6	10
8	38·2	34	11·4	14
9	37·2	24	10·1	4
10	37·2	22	1·6	4
11	37·6	22	19·4	9
12	37·2	18	15·2	3
13	37·8	27	10·5	13
14	37·0	25	11·8	28
15	37·7	35	11·1	28
16	38·2	23	6·6	19
17	36·6	28	19·5	18
18	37·2	21	10·4	1
19	37·4	25	7·9	19
20	36·6	29	15·7	9

WBC, white blood cell

and correlations, by ABSTAT statistical package (Anderson Bell and Parker Co.) on an IBM XT personal computer. Means will be quoted with the standard error of the mean.

Table 3 *Energy expenditure as calculated by four formulae compared for each of the 20 patients*

Patient no.	Resting energy expenditure (kcal/day)			
	HB	EF	CR	MGM
1	1059	1034	1141	1051
2	1098	1340	1296	2199
3	1855	2044	1196	2421
4	1255	1047	1081	2695
5	1287	1400	1238	794
6	1235	1263	1047	1168
7	1276	1380	1016	1592
8	1232	1345	1319	1180
9	1350	1515	1284	919
10	1526	1565	1182	1317
11	1091	976	1245	820
12	1368	1410	1186	976
13	1558	1764	1455	2235
14	1596	1773	1624	1441
15	1527	1598	1458	1335
16	1496	1473	1231	1531
17	1035	992	1133	807
18	1033	1021	1107	941
19	992	926	1071	740
20	1606	1544	1318	1475

HB, the Harris–Benedict equation; EF, empirical formula; CR, creatinine formula; MGM, MGM II indirect calorimeter

Results

Twelve women and eight men completed the study. Their mean age, 61·7±2·8 years, is typical of many surgical intensive care units. Their average temperature of 37·5±0·1°C, urinary urea nitrogen excretion 8·9±1·2 g/24 h, albumin concentration 24±1 g/l, white cell count $13{\cdot}4\pm2{\cdot}3\times10^3/\text{mm}^3$ and band forms 14·2±2·7 per cent confirm a stressed population. The remainder of their clinical data are shown in *Tables 1*, *2* and *3*.

The average daily energy expenditure calculated by the urinary creatinine formula was 1231±34 kcal/day, by the Harris–Benedict equation was 1324±53 kcal/day and by the empirical formula was 1370±68 kcal/day. These were found not to be different from the measured value 1382±130 kcal/day by one-way analysis of variance. The correlation coefficients relating the MREE to the calculated values were as follows: creatinine formula, $r=0{\cdot}14$; empirical formula, $r=0{\cdot}45$; and the Harris–Benedict formula, $r=0{\cdot}48$. Thus whereas the Harris–Benedict formula ($P<0{\cdot}05$) and empirical formula ($P<0{\cdot}05$) correlate well with REE, the creatinine formula does not.

Using multiple linear regressions, REE was found to be significantly related to sex ($P<0{\cdot}003$), weight ($P<0{\cdot}003$), white cell count ($P<0{\cdot}003$) and 24-h urinary creatinine ($P<0{\cdot}05$), and an equation relating these values predicts 76 per cent of the variability in the MREE.

$$\text{REE}=620{\cdot}2+27{\cdot}3\times W+28{\cdot}8\times \text{WBC}-603{\cdot}2\times \text{sex}-0{\cdot}66\times Cr \quad (r=0{\cdot}87)$$

where W is weight in kg, WBC is white cell count in 1000 cells/mm^3, male is 1 and female is 2, and Cr is urinary creatinine in g/24 h

Reducing the variables further, an equation relating just three could predict 68 per cent of the variability in MREE ($r=0{\cdot}82$).

$$\text{REE}=613+19{\cdot}7\times W-525{\cdot}6\times \text{sex}+28{\cdot}7\times \text{WBC}$$

Further reducing the variables to two was still superior to the Harris–Benedict formula or empirical formula in our patient population. Using weight and white blood cell count, r was 0·72; and using sex and white blood cell count, r was 0·73. The best single variable was found to be sex with an r value of 0·65, and then weight with an r value of 0·45. Interestingly, weight is responsible for 80 per cent of the variability in the Harris–Benedict formula.

Discussion

A number of formulae have been proposed for the estimation of resting energy expenditure[2,3,5,8] and in one way or another these relate energy expenditure to body cell mass. Harris and Benedict and others[2,5] have used weight, height, age and sex to determine REE, and these variables have been shown to correlate significantly with body cell mass ($P<0{\cdot}001$)[9]. However, Roza and Shizgal, in their critique of the Harris–Benedict formula[9] showed that in fact body cell mass can be independent of both age and sex in hospitalized patients, and that height, age and sex reflect only the usual relationship of weight to body cell mass.

Shanbhogue *et al.* related urinary creatinine to REE[2]. They pointed out that body cell mass has been related to 24-h urinary creatinine excretion in several isotope dilution studies[10–12]. Furthermore, since creatinine excretion is almost entirely from muscle, and muscle is a relatively stable proportion of body cell mass, they proposed a constant relationship between REE and 24-h creatinine excretion. An equation relating REE to 24-h creatinine excretion correlated significantly with the measured energy expenditure ($P<0{\cdot}001$) in their study of non-stressed individuals who varied in their nutritional status from malnourished to obese[2].

Others have suggested that both malnutrition[9] and stress[3,13,14] play an important part in increasing the REE. Trauma and burns were shown to increase the REE significantly[14] and it is suggested that this may be due to an increase in catabolic rate[3]. This has led to the commonly used formula[3] for energy replacement in stressed patients of 1·75 × the Harris–Benedict formula. However, some debate exists about the significance of stress in many common situations, as the response in REE has been shown to be variable[13]. No differences were found in the REE in major surgery or sepsis in one study[14], but in the same study both trauma and burns significantly increased the energy requirements Several recent papers have shown that no multiplication factors are needed to relate the Harris–Benedict formula to the REE in stressed patients[15–17] and that the Harris–Benedict formula itself may be an over-estimation in the healthy population[18].

Our study confirms that the Harris–Benedict formula provides a good mean estimate of REE in the stressed population ($P<0{\cdot}05$) and that it does not need a multiplication factor even though it assumes the fasting state which it is generally not reasonable to produce in the critically ill However, it proved less predictive in the individual patient ($r=0{\cdot}48$) Since weight is responsible for 80 per cent of the variability in the Harris–Benedict formula, using weight alone ought to be nearly as predictive as the formula. We found this to be the case. 22 times the weight in kilograms (or 10 × weight in pounds) also gives a good mean estimate ($P<0{\cdot}05$), but again this is not as predictive in the individual case ($r=0{\cdot}45$).

The creatinine formula[2] was of limited predictive value in our patient population ($r=0{\cdot}14$). The poor predictive value of the urine creatinine alone may also be due to the lower muscle mass, in relation to total lean body mass, in our predominantly malnourished and elderly surgical intensive care unit patients. A major contributing factor must be the varying degree of stress in these patients which such a formula would not be expected to measure. This hypothesis is supported by the excellent r value (0·87) when a stress variable, white blood cell count, is included along with urine creatinine, sex and weight. The white blood cell count significantly correlated with REE ($P<0{\cdot}003$) and it persisted in significance even when only two variables were utilized. The predictive value was reasonable in combination with either weight ($r=0{\cdot}72$) or sex ($r=0{\cdot}73$). Both these combinations were far superior to the Harris–Benedict formula.

One interpretation for these findings is that the major components determining the resting energy expenditure of malnourished patients who are stressed is the amount of lean tissue and the degree of stress. Weight over-estimates lean tissue in stressed malnourished patients, such that the decrement in energy expenditure due to this is approximately equalled by the increase of energy expenditure resulting from stress. Thus, weight and the Harris–Benedict formula fortuitously predict the total energy expenditure, but only on a population basis. Where a better estimate of lean tissue is used, for example urinary creatinine excretion, the good correlation found in malnourished patients is not found when stress is also present, i.e. the creatinine equation. Only when creatinine is only one component of the equation, with sex and weight to further define lean tissue, and where white count reflects stress, could a good estimate of resting energy expenditure be derived

In a randomized study in critically ill patients[19], which also included some young patients with multiple traumatic injuries, a similar amount of calories were needed as in our predominantly elderly and non-traumatized patients, when measuring their REE (21–25 kcal/kg), despite their being given 40 kcal/kg In our study 30 kcal/kg would have given sufficient calories for 90 per cent of the patients; however, in 20 per cent of our patients this would give an excess of 1000 kcal and it would be double the needs of 15 per cent. Thus, we would advocate 30 kcal/kg only for non-ventilated patients and for patients in whom excessive intake is not of major concern, e.g. patients who would not be harmed by overfeeding by a moderate amount (that is, unstressed, malnourished patients with otherwise good organ function such as anorexia nervosa patients)

It can be seen from the above discussion that none of the conventional equations is sufficiently accurate for the individual Body cell mass and stress are of importance in relating REE to the patient's needs, but the simple empirical formula is as good a population estimate of REE and is easier to perform than most conventional formulae. A prospective trial in a larger number of individuals would be necessary before one could promote the use of the empirical formula equation developed in this study. This study did not, of course, address the validity of the quoted literature in relation to overfeeding and weaning difficulties, as it has been the policy of this unit to feed according to the MREE. Interestingly, all four of the patients who would have received twice their caloric needs, if given 30 kcal/kg, proved to be patients with weaning difficulties. In addition, one patient who had had a liver transplant and was receiving immunosuppressant drugs had difficulty controlling diabetes mellitus and had problems with sepsis, both of which are aggravated by excessive calories. Therefore, since portable indirect calorimeters are now easily available and are reliable, simple to use and accurate[6], we would advocate their use, particularly in the measurement of REE in the ventilated patient receiving nutritional support who presents with a weaning difficulty, is severely malnourished (i.e > 20 per cent weight loss), where energy needs are most poorly estimated, is more prone to complications of overfeeding (e.g. diabetes, impaired lung or liver function), or has been receiving total parenteral nutrition for a prolonged period (> 2 weeks).

References

1. Askanazi J, Weissman C, Rosenbaum H *et al.* Nutrition and the respiratory system *Crit Care Med* 1982; **10**: 163–72.
2. Shanbhogue RCK, Bistrian BR, Swenson S *et al.* 24-hour creatinine. a simple technique for estimating resting energy expenditure in normal population and the hospitalized patients. *Clin Nutr* (in press).
3. Rutten P, Blackburn GL, Flatt JP *et al.* Determination of optimal hyperalimentation infusion rate. *J Surg Res* 1975; **18**· 477–83.
4. Feurer I, Mullen SL Bedside measurements of resting energy expenditures and respiratory quotient via indirect calorimetry. *Nutr Clin Pract* 1986; **1**· 43–9.
5. Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism in Man.* Publication No. 279 of the Carnegie Institute of Washington, 1919.
6. Westenskow DR, Cutler CA, Wallace WD Instrumentation for monitoring gas exchange and metabolic rate in critically ill patients. *Crit Care Med* 1984; **12**: 183–7
7. Bursztein S, Saphar P, Glasser P *et al* Determination of energy metabolism from respiratory function alone. *J Appl Physiol* 1977; **62**: 117–19
8. Rainey-MacDonald CG, Holliday RL, Wells GA. Normograms for predicting resting energy expenditure of hospitalized patients. *JPEN* 1982; **6**: 59–60.
9. Roza AM, Shizgal HM. The Harris–Benedict equation reevaluated: resting energy requirements and the body cell mass *Am J Clin Nutr* 1984, **40**: 168–82.
10. Cunningham JJ. Body composition and resting metabolic rate: the myth of feminine metabolism. *Am J Clin Nutr* 1982; **36**: 732–26.
11. Forbes GB, Bruining GJ. Urinary creatinine excretion and lean body mass. *Am J Clin Nutr* 1976; **29**. 1359–66.
12. Miller AT, Blyth CS. Estimations of lean body mass and fat from basal oxygen consumption and creatinine excretion. *J Appl Physiol* 1952; **5**· 73–8
13. Kinney JM, Roe CF Caloric equivalent of fever, patterns of postoperative response *Ann Surg* 1962; **156**: 610–22.
14. Duke JH, Jorgensen SB, Broell JR *et al* Contribution of protein to caloric expenditure following injury *Surgery* 1970; **68**: 168–74.
15. Mann S, Westenskow DR, Houtchens BA. Measured and predicted caloric expenditure in the acutely ill. *Crit Care Med* 1985; **13**: 173–7.
16. Chan ATH, Fleming CR, O'Fallon WM *et al.* Estimated *versus* measured basal energy requirements in patients with Crohn's disease. *Gastroenterology* 1986, **91**: 75–8.
17. Quebbeman EJ, Ausman RK, Schneider TC. A reevaluation of energy expenditure during parenteral nutrition. *Ann Surg* 1982; **195**: 282–6.
18. Daly JM, Heymsfield SB, Head CA *et al.* Human energy requirements: overestimation by widely used prediction equations. *Am J Clin Nutr* 1985; **42**: 1170–4.
19. Baker JP, Detsky AS, Stewart S *et al.* Randomized trial of total parenteral nutrition in critically ill patients: metabolic effects of varying glucose–lipid ratios as the energy source. *Gastroenterology* 1984, **87**: 53–9.

Paper accepted 22 May 1988

Case report

Br. J. Surg. 1988, Vol. 75, September, 878–879

Retroperitoneal extravasation from perforated duodenal ulcer

W. H. Weston-Davies, M. Pertkiewicz and B. Szczygiel

Squibb Surgicare Ltd, Squibb House, Middlesex, UK and Department of Gastro-enterological Surgery, University of Warsaw, Warsaw, Poland

Correspondence to: Mr W. H. Weston-Davies, Squibb Surgicare Ltd., Squibb House, 141/149 Staines Road, Hounslow, Middlesex TW3 3JA, UK

Four cases are described in which perforation of duodenal ulcers led to extravasation of duodenal contents to the retroperitoneal space. The diagnosis is difficult and is rarely made before operation. Even at operation it may be missed in which case the mortality is high.

Case reports

Case 1

A 79-year-old man presented with an 8-h history of central and right iliac fossa pain and vomiting. He was dehydrated, shocked and had signs of peritonitis with maximal guarding in the right iliac fossa An initial diagnosis of perforated acute appendicitis was made At operation the most immediate and striking finding was a large collection of fluid lying extraperitoneally in the right iliac fossa and extending up behind the caecum. When aspirated the fluid contained 200 ml of bile-stained intestinal contents. In addition there was a small amount of turbid fluid lying within the peritoneal cavity. The appendix was normal

Further exploration revealed an anteriorly situated ulcer of the second part of the duodenum from which there was a small perforation into the peritoneal cavity. It was also apparent that most of the extravasated duodenal contents had tracked back to the retroperitoneal space between the layers of the duodenal wall and thence to the retrocaecal space. Laparotomy was otherwise normal.

The ulcer was oversewn and an omental patch applied. The peritoneum overlying the collection in the right iliac fossa was incised and the retrocaecal space was drained via the abdominal cavity. Before closure the abdomen was irrigated with 100 ml of 2·5 per cent noxythiolin solution Antibiotics were given postoperatively. Apart from a prolonged paralytic ileus and a respiratory infection, recovery was uneventful.

Case 2

A 43-year-old man presented with a 12-h history of central and lower right quadrant abdominal pain and vomiting. He had several years history of intermittent symptoms of a similar nature. On examination he was shocked, the abdomen was tense and distended and bowel sounds were absent. An initial diagnosis of perforated acute appendicitis was made. At operation an extensive collection of bile-stained fluid was discovered extending retroperitoneally from the horizontal part of the duodenum through the right iliac fossa to the true pelvis, associated with a perforated ulcer of the posterior wall of the duodenum 12 mm in diameter, situated 3 cm from the pylorus. A Billroth I partial gastrectomy was undertaken and the retroperitoneal space was drained Apart from a postoperative wound infection he made a good recovery.

Case 3

A 49-year-old alcoholic man presented with a 7-day history of abdominal pain radiating into the testicles, nausea, vomiting and absolute constipation He had been anuric for 24 h He was prostrated, shocked and septicaemic and had signs of generalized peritonitis. Abdominal X-ray revealed free intraperitoneal gas. At laparotomy free purulent fluid was present in the peritoneal cavity, particularly in the right upper quadrant, but no obvious source of perforation was discovered in the stomach or duodenum A pelvic mass, presumed to be a carcinoma of the rectosigmoid colon, was discovered with an associated proximal perforation. Resection and primary anastomosis were carried out and the abdomen was closed with drainage.

The patient died 6 days later of overwhelming sepsis. Autopsy revealed a posterior ulcer of the second part of the duodenum which communicated freely with a large retroperitoneal collection. This in turn communicated with a small perforation in the mesentery of the sigmoid colon. The rectosigmoid mass proved to be inflammatory in nature.

Case 4

A 59-year-old woman presented with a 2-day history of generalized abdominal pain and progressive paralytic ileus. At laparotomy an almost total transection of the second part of the duodenum was

0007–1323/88/090878–02$3 00

discovered which communicated with a large retroperitoneal collection extending up to the hilum of the liver and downwards to the brim of the pelvis. A Rydygier–Zaorski resection was performed and the retroperitoneal space was drained. Her postoperative course was complicated by pneumonia which culminated in death from cardiorespiratory failure.

Discussion

Retroperitoneal perforation is a rarely diagnosed complication of duodenal ulcer. Hashmonai *et al.*[1] in 1971 found only nine definite cases in the literature since 1865, to which they added four of their own[2–5]. Since then ten further cases have been reported including the present ones[6–9].

The 13 cases quoted by Hashmonai *et al.* included 5 reports by Petren[10] of cases that had occurred at a time when surgical and diagnostic techniques were less well developed. Of these five, all of whom died, only three were operated upon. Seventeen of the remaining cases cover the years since 1947 when better diagnostic techniques, antibiotics and improved surgical management were available. Despite this the mortality during this period has been 47 per cent and the morbidity in terms of reoperation and sequelae has been considerable.

The diagnosis of retroperitoneal perforation may be difficult even at operation, particularly if the leak has been relatively small and no obvious retrocaecal collection is present. In nine cases it was made at the initial operation, in two postoperatively and in five at autopsy. The commonest misdiagnosis was appendicular disease (eight) and other misdiagnoses included perinephric abscess, retrocolic abscess and chronic duodenal ulcer.

In the nine cases in which the correct diagnosis was made at the initial operation, drainage of the collection was performed in all but one, in which the site of the abscess was not located. Closure of the perforation was attempted in only five cases including three of the present cases, and duodenal diversion by gastrojejunostomy in a further two (in one of these it was combined with an end duodenostomy as a second-stage procedure[2]). These authors considered that drainage of the collection alone was insufficient and that closure of the perforation and diversion of the duodenal flow should also be attempted.

Case 1 illustrates that the ulcer does not have to be posteriorly sited for retroperitoneal extravasation to occur. A number of other authors have described extravasation of gas to the abdominal wall or mediastinum associated with anteriorly situated duodenal ulcer[11–14]. A flap-valve mechanism was postulated by Vigyazo to explain this phenomenon, whereby gas or duodenal contents might be forced into the subserosal layers of the duodenal wall and thence into the retroperitoneal space, possibly as a result of a sudden rise in intraluminal pressure during vomiting. It is of note that vomiting in the period before admission was a striking feature.

Modern diagnostic techniques including detailed radiological examination of the upper gastrointestinal tract and retroperitoneal region should make the diagnosis feasible providing that awareness of the possibility exists. Early exploration and drainage are imperative and it is suggested that a detailed examination of the duodenum, including mobilization and, if necessary, duodenotomy, be undertaken in all cases of unexplained retroperitoneal abscess or overt retrocaecal collection.

Acknowledgements

The authors would like to thank Mr Ian Todd PRCS for permission to publish details of the first of these cases.

References

1. Hashmonai M, Abrahamson J, Erlik D, Schramek A Retroperitoneal perforation of duodenal ulcers with abscess formation: a report of four cases and survey of the literature *Ann Surg* 1971; **173** 409–14
2. Britt LG, Wolf RY Postbulbar ulcer with retrocecal abscess; a case report. *Arch Surg* 1966; **92**: 98–100.
3. Koenig TS, Culver GJ. Retroperitoneal perforation of the duodenum—a case report *Radiology* 1947; **48**: 164–7
4. Kirilova TS. Perforation of duodenal ulcer in the retroperitoneal space. *Khirurgiia* (*Mosk*) 1961; **37**. 114
5. Basile R. Perforazione retroperitoneale di ulcera duodenale. *Fracastoro* 1963, **56**: 106.
6. Wulsin JH. Peptic ulcer of the posterior wall of the stomach and duodenum with retroperitoneal leak. *Surg Gynecol Obstet* 1972, **134**: 425–9.
7. Ferreira V, Garcia-Lisbona JR, Martinez A, Perez-Ruiz L. Retroperitoneal perforation of a duodenal ulcer. *Semaines des Hopitaux* 1979; **55**: 43–4.
8. Szczygiel B, Pertkiewicz M, Switka S, Rucinski J. Perforation of duodenal ulcer into the retroperitoneal space. *Pol Przegl Chir* 1979; **51**: 753–7.
9. Sturup J, Raahave D. Retroperitoneal perforation of duodenal ulcer. *Ann Chir Gynaecol* 1985, **74** 299–300
10. Petren G. On retroperitoneal perforation of duodenal ulcer. *Ann Surg* 1915; **61**: 414–22.
11. Oetting HK, Kramer NE, Branch WE Subcutaneous emphysema of gastrointestinal origin. *Am J Med* 1955, **19** 872–86.
12. Vigyazo J. Subcutaneous emphysema in ulcer perforation *JAMA* 1926; **87**: 986.
13. Podlaha J. Zur frage des subkutanen emphysem bei perforierten gastroduodenalen gechwuren *Zentralbl Chir* 1926; **53**. 2839–41.
14. McCorkle M, Stevenson J. Subcutaneous emphysema associated with perforated peptic ulcer. *Surgery* 1937; **2**· 930–6.

Paper accepted 13 March 1988

Br. J. Surg. 1988, Vol. 75, September, 880–882

Grip strength: a measure of the proportion of protein loss in surgical patients

J. A. Windsor and G. L. Hill

Department of Surgery, University of Auckland School of Medicine, Auckland, New Zealand

Correspondence to.
Professor G. L. Hill, Department of Surgery, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand

Measurements of voluntary hand grip strength (GS) are a sensitive predictor of postoperative complications. The loss of body protein is thought to be important in the development of these postoperative complications, but the relationship between GS and body protein status has not been studied. We have measured GS (by hand dynamometry), total body protein (indirectly by mid-arm muscle circumference, and directly by in vivo *neutron activation analysis) and the proportion of protein loss (protein index) in 80 patients with gastrointestinal disease and 87 normal volunteers. Using regression analysis, a matched study and clinical decision analysis, it has been demonstrated that GS is a sensitive measurement of the degree of protein loss. The results support more widespread use of GS measurements in the identification of patients at high risk of postoperative complications and in the monitoring of patient response to nutritional intervention.*

Keywords: Grip strength, nutritional assessment, protein depletion

Voluntary hand grip strength (GS) measurements have been shown to be a more sensitive predictor of serious postoperative complications than traditional anthropometric and biochemical assessment of nutritional status in surgical patients[1–4]. Protein depletion is an important factor in the development of postoperative complications[5–7] especially when it is associated with an impairment of important physiological functions[8,9]. Protein depletion also results in a reduction in skeletal muscle strength[10]. Unfortunately, protein depletion is often diagnosed by measuring the muscle mass of the arm[1,11], which in itself must correlate with arm strength irrespective of the degree of protein depletion. There are no studies which examine the relationship between GS and a direct measurement of body protein status.

In this study our hypothesis was that the sensitivity of GS as a predictor of postoperative complications resulted not only from the fact that it reflected the total amount of protein stores present in a given patient, but because it was also a measure of the proportion of protein that a patient had lost. We therefore measured grip strength, total body protein and the proportion of protein loss in a series of patients and normal volunteers.

Patients and methods

Subjects

Between April 1985 and July 1986, 80 surgical patients (median age 59 years, range 18–85 years, 41 men, 39 women) with a range of major gastrointestinal disorders (31 per cent benign, 69 per cent malignant) had measurements of GS and body protein status on the day before starting intravenous nutrition ($n = 12$) or having a major gastrointestinal resection ($n = 68$). A total of 87 normal volunteers (median age 36 years, range 19–82 years, 44 men, 43 women) had the same measurements of GS and body protein status.

Measurement of grip strength

Voluntary hand grip strength was measured in the dominant hand using a vigorimeter (Ortopedia, FRG) with a 50mm bulb. The seated patient was instructed to squeeze the bulb quickly and maximally to give a reading on the dial in kilopascals. Three readings were made at 15s intervals and the best of the three attempts recorded as the maximum GS. The coefficient of variation for this method was 5·45 per cent and the normal range for men was 100–180kPa and for women 55–100kPa[12]

Measurement of body protein stores

The mid-arm muscle circumference, which is used as an indirect measure of body protein stores, was derived from the measurements of triceps skinfold thickness and mid-arm circumference[11]. The direct measurements of total body protein (TBP) were made by prompt gamma *in vivo* neutron activation analysis[13].

Measurement of the proportion of body protein loss

A protein index (PI = measured divided by predicted TBP) was used as a measure of the proportion of body protein loss[14]. The predicted TBP was derived by multiple regression analysis based on the age, height and sex of local normal volunteers. Protein depletion was defined as a protein index of 0·77 or less, which represents at least two standard deviations from unity in a study of normal volunteers[14].

Statistical methods

Linear regression analysis (correlation coefficient) and one-way analysis of variance (F test) were used to evaluate the relationship between GS and measures of body protein status. A paired Student's t test was used to test for significance in the matched study. Clinical decision analysis was carried out by standard methods[15], and the degree of significance was determined by the χ^2 test (2×2).

Results

Regression analysis

Table 1 shows the results of the regression analyses and analyses of variance for the measurements of grip strength and body protein status (MAMC, TBP and protein index) in the 80 patients. It can be seen that a significant relationship exists for each analysis. *Figure 1* shows the regression of GS *versus* protein index for the patients.

Table 1 *Regression analyses and analyses of variance for the measurements of grip strength and mid-arm muscle circumference, total body protein, and protein index in the 80 patients*

	Correlation coefficient	Coefficient of variation	F test	P
GS *versus* MAMC	0·62	20·4	48·8	<0·0001
GS *versus* TBP	0·77	16·5	114·7	<0·0001
GS *versus* PI	0·56	21·6	35·1	<0·0001

GS, grip strength; MAMC, mid-arm muscle circumference; TBP, total body protein; PI, protein index

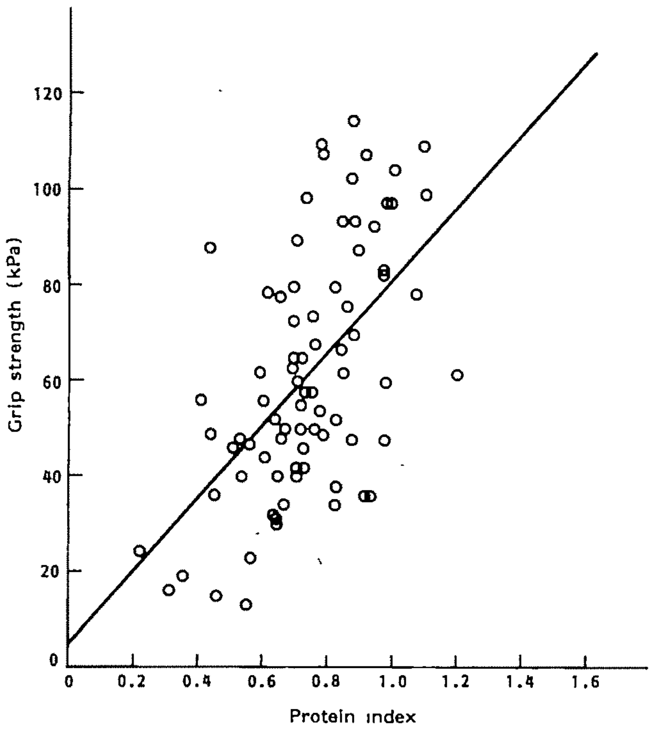


Figure 1 *Regression of grip strength and protein index* (r=0·56, *standard error*=20·4) *in the 80 patients*

Table 2 *The measures of the proportion of body protein loss (protein index) and grip strength for 32 normal volunteers and 32 surgical patients matched for sex, age, height and total body protein (measured by* in vivo *neutron activation analysis)*

	Normal subjects	Patients	*P*
Sex (M:F)	18:14	18:14	n.s.
Age (years)	47 (19–81)*	52 (20–85)	n.s.
Height (cm)	168·9±1·7†	170·7±1·5	n.s.
MAMC (mm)	266·4±5·0	259·1±6·2	n.s.
Measured TBP (kg)	9·51±0·42	9·51±0·43	n.s.
Predicted TBP (kg)	10·1±0·41	10·8±0·38	n.s.
Protein index	0·94±0·10	0·88±0·17	<0·05
Grip strength (kPa)	93·2±6·8	74·1±4·1	<0·025

* Mean (range); † mean±s.e.m., MAMC, mid-arm muscle circumference; TBP, total body protein

Matched study

In order to examine the relationship between GS and the proportion of body protein loss (protein index) more specifically, 32 patients and 32 normal volunteers were retrospectively matched for TBP (±500 g), age (±5 years), height (±5 cm), and sex (18 men, 14 women), and were then compared for the protein index and GS. *Table 2* shows that although the normal volunteers and patients were not significantly different for age, height, sex and total body protein, they were significantly different for the protein index ($P<0·05$) and grip strength ($P<0·025$). Also shown in *Table 2* are the measurements of mid-arm muscle circumference and predicted TBP for the two groups, which are not significantly different.

Decision analysis

In order to evaluate how well the measurement of GS is able to identify patients with a significant loss of body protein the data were subjected to clinical decision analysis[15]. The cut-off values used for the measurements of GS were those published by Pettigrew and Hill[12] and these selected approximately one-quarter of the total number of patients. *Table 3* shows that the majority of patients with protein depletion registered a low GS measurement (the sensitivity for men was 68·7 per cent and for women 51·6 per cent); the majority of patients without protein depletion registered a high GS measurement (the specificity for men was 88·4 per cent and for women was 90·1 per cent), and the majority of patients with a low GS measurement had protein depletion (the positive predictive value for men was 57·8 per cent and for women 76·1 per cent). The false assurance rate, which represents those with protein depletion who registered a high GS measurement, was 7·5 per cent in men and 24·5 per cent in women.

Discussion

This study confirms, by direct measurement, that there is a relationship between a patient's grip strength and total body protein. Previously, this has only been suggested on the basis of indirect anthropometric measurement techniques. In addition, this study demonstrates a significant relationship between grip strength and the proportion of protein loss (protein index).

Grip strength measurements are a 'prototype' for measurements of body function in clinical nutritional assessment. There is a trend towards viewing protein malnutrition in terms of its impact on important body functions[16]. These functions, which include skeletal muscle, respiratory, immunological, hepatic, or cardiac function, all have some reserve capacity. This reserve represents the proportion of protein that can be lost before there is measurable and also clinically relevant impairment of function. For this reason, it appears that it is more important to obtain a measurement of the proportion of protein loss than the amount of total body protein remaining.

The relationship between GS and the proportion of protein loss might be accounted for by the fact that with malnutrition protein is preferentially lost from muscle[17], with the result that a reduction in muscle strength may occur before measurable changes in other parameters of nutritional status. It might be argued that the relationship between GS and protein loss exists because of significant correlations which can be demonstrated between GS and age, height and sex, the three variables used to derive the denominator of the protein index (predicted TBP). However, this is unlikely as these three variables are controlled for in the matched study (*Table 2*).

GS measurements have been used as an indirect measure of body protein stores because the protein content of muscle has been shown to correlate with its strength[17] and because arm muscle area, which is significantly correlated with GS[18,19] has been shown to be a valid index of skeletal muscle mass[11].

There are many factors, in addition to body protein status, that might influence GS measurements and in some cases clinical outcome as well. These include age, sex, posture, circadian rhythm, psychological state, sedative drugs, the

Table 3 *A decision analysis for the detection of a significant loss of body protein (protein index* ≤0·77) *using the grip strength measurements in male and female patients*

	Grip strength	
	Men	Women
n	85	82
Cut-off value (kPa)	64	47
Patients selected (%)	22·1	25·6
Sensitivity (%)	68·7	51·6
Specificity (%)	88·4	90·1
Positive predictive value (%)	57·8	76·1
Negative predictive value (%)	92·4	75·4
Overall predictive value (%)	84·7	75·6
False assurance rate (%)	7·5	24·5
P value (χ^2)	<0·001	<0·001

available treatment options and the primary disease process[20]. Martin *et al.*[20] found that a decrease in grip strength was associated with the presence of disease and suggested that this might be due to pain, circulatory changes with associated alterations in the concentrations of electrolytes and metabolites, drug administration and/or decreased motivation to perform the test. These factors do not need to detract from the usefulness of GS measurements, as they have a direct bearing on the patient's ability and willingness to co-operate with many aspects of surgical convalescence (including physiotherapy and mobilization). While the effects of age, posture, drugs and the time of day have been controlled for in this study, the comparisons between patients and normal volunteers does not control for the presence of disease as a factor that might influence the measurement of GS.

The development of modern techniques of nutritional support has meant that the adverse effect of malnutrition on a patient's clinical course might be reversible. This has resulted in a renewed interest in developing simple clinical approaches (like the measurement of GS) to selecting patients who, because of the increased risks associated with the loss of body protein, warrant nutritional intervention.

Being a measure of a physiological function, the measurement of GS adds a new dimension to the biochemical and anthropometric techniques of nutritional assessment used so widely today. Because it is simple to perform, is unsurpassed as a single predictor of postoperative complications[1–4], and has now been shown (by direct measurement) to be a measure of the proportion of protein depletion, there is a strong argument for the routine use of GS measurements in the nutritional assessment of surgical patients. It might be that a careful clinical assessment of the patient's nutritional and functional status[9], incorporating a clinical assessment of grip strength, would be the most sensitive, specific and practical way of selecting patients at high risk of postoperative complications and those who are likely to benefit from pre-operative repletion.

Acknowledgements

We wish to acknowledge the help of Dr A. Beddoe, Dr J. Sutcliffe, Miss S. Gasgoigne and Miss S. McWilliams in the measurement of patients and volunteers. J.A.W. is a Medical Research Council of New Zealand training fellow

References

1. Klidjian AM, Foster KJ, Kammerling RM, Cooper A, Karran SJ. Relation of anthropometric and dynomometric variables to serious postoperative complications. *Br Med J* 1980; **281**: 899–901
2. Klidjian AM, Archer TJ, Foster KJ, Karran SJ. Detection of dangerous malnutrition. *J Parent Ent Nutr* 1982, **6**: 119–21.
3. Twiston Davies CW, Moody Jones D, Shearer JR. Hand grip—a simple test for morbidity after fracture of the neck of femur. *J R Soc Med* 1984; **77**: 833–6.
4. Hunt DR, Rowlands BJ, Johnston D. Hand grip strength—a simple prognostic indicator in surgical patients. *J Parent Ent Nutr* 1985; **9**· 701–4.
5. Kammerling K, Foster KJ, Karran SJ. Protein depletion and recovery from surgical operation. *Br J Surg* 1978; **165**: 365.
6. Buzby GP, Mullen JL, Matthew DC *et al.* Prognostic nutritional index in gastrointestinal surgery. *Am J Surg* 1980; **139**: 160–7.
7. Windsor JA, Hill GL. Protein depletion and surgical risk. *Aust NZ J Surg* 1988 (in press).
8. Jeejeebhoy JN. The functional basis of assessment. In: Kinney J, Jeejeebhoy KN, Hill GL, eds. *Nutrition and Metabolism in Patient Care* Philadelphia: W.B Saunders, 1988: 739–51.
9. Windsor JA, Hill GL. Weight loss with physiological impairment: a basic indicator of surgical risk. *Ann Surg* 1987 (in press)
10. Lopes J, Russell D, Whitwell J *et al.* Skeletal muscle function in malnutrition. *Am J Clin Nutr* 1982; **36**: 602–10.
11. Heymsfield SB, McManus C, Stevens V, Smith J Muscle mass: reliable indicator of protein-energy malnutrition and outcome. *Am J Clin Nutr* 1982, **35**: 1192–9.
12. Pettigrew RA, Hill GL. Indicators of surgical risk and clinical judgement *Br J Surg* 1986; **73**· 47–51.
13. Knight GS, Beddoe AH, Streat SJ, Hill GL. Body composition of two human cadavers by neutron activation and chemical analysis. *Am J Physiol* 1986, **250**: E179–E185.
14. Beddoe AH, Streat SJ, Hill GL Hydration of fat-free body in protein-depleted patients *Am J Physiol* 1985, **249**: E227–233.
15. Weinstein MC, Fineberg HV *Clinical Decision Analysis.* Philadelphia: W. B. Saunders Co , 1980. 75–127.
16. Grant JP. Nutritional assessment in clinical practice. *Nutr Clin Pract* 1986; **2**: 3–11
17. Daniel PM, Pratt OE, S'Argo E. Metabolic homeostatic role of muscle and its function as a store of protein. *Lancet* 1977; **2**: 446–8.
18. Grant JP. Current practices of nutritional assessment—functional assessment. In: Levenson SM, ed. *Nutritional Assessment—Present Status, Future Directions and Prospects.* Ohio: Ross Laboratories, 1981: 137–141.
19. Harries AD. A comparison of hand grip dynamometry and arm muscle size amongst Africans in north-east Nigeria. *Hum Nutr· Clin Nutr* 1985; **390** 309–13.
20. Martin S, Neale G, Elia. M. Factors affecting maximal momentary grip strength. *Hum Nutr. Clin Nutr* 1985, **39**. 137–47.

Paper accepted 21 March 1988

Br. J. Surg. 1988, Vol. 75, September, 883–886

Neutrophil degranulation and increased pulmonary capillary permeability following oesophagectomy: a model of early lung injury in man

G. M. Rocker,
M. S. Wiseman,
D. Pearson* and
D. J. Shale

Respiratory Medicine Unit and
**Department of Medical Physics,*
City Hospital, Hucknall Road,
Nottingham NG5 1PB, UK

Correspondence to:
Dr D J Shale

In nine subjects undergoing oesophagectomy a transient but significant increase in pulmonary vascular permeability to transferrin was detected in both lungs 8 h after surgery. It coincided with a significant increase in plasma lactoferrin, evidence of intravascular and intra-alveolar neutrophil elastase release and with arterial hypoxaemia. The postoperative state in these patients had intravascular and pulmonary features often associated with the adult respiratory distress syndrome, and might be a useful model for the study of the early inflammatory events underlying lung injury in man.

Keywords: Adult respiratory distress syndrome, oesophagectomy, neutrophils, radioisotopes, transferrin

The major clinical manifestation of severe lung injury in man is the adult respiratory distress syndrome (ARDS), a severe form of respiratory failure associated with a protein-rich pulmonary oedema[1,2]. The key feature appears to be diffuse pulmonary microvascular injury initiated by a severe systemic inflammatory response. Many components of this response have been investigated, but interest has focused on the role of the neutrophil as a major effector cell mediating endothelial damage and increased permeability to plasma proteins[3–7]. In models of ARDS in animals, there is a clear relationship between neutrophil function and increased pulmonary capillary permeability[8–10], but this relationship in man is less certain because the timing of initiation of the inflammatory response is usually unknown. In addition there is evidence that similar pulmonary vascular injury may occur in the absence of neutrophils[11,12]. In human studies, ARDS unpredictably affects only a small proportion of patients at risk and, prospective studies of the evolution of the inflammatory response are therefore difficult[13,14]. The variable time period between the insult and attainment of criteria for the diagnosis of ARDS[13] is a further factor which tends to limit studies of pathophysiological mechanisms to established ARDS, where the inflammatory findings may not be the same as those at onset of lung injury.

The postoperative state shares features associated with established ARDS: activation of the neutrophil and the complement and coagulation systems occurs in both, secondary infection is common in ARDS and postoperative pulmonary insufficiency and infection are the major causes of morbidity and mortality after surgery[15]. To seek a model of lung injury in man, neutrophil degranulation (as a feature of activation) and pulmonary vascular permeability were therefore studied in patients sustaining lung injury during transthoracic oesophagectomy.

Patients and methods

Nine consecutive patients aged <75 years (eight men, one woman) undergoing oesophagectomy (four left thoracotomy, five right thoracotomy) were studied. All had normal chest radiographs before surgery for histologically proven carcinoma of the oesophagus. Each patient acted as their own control reducing any influence of malignancy or variation between anaesthetic regimens on the inflammatory response. All patients gave informed consent to the study which had local ethical committee approval. Within 72 h before surgery pulmonary capillary permeability to transferrin was determined using a double isotope method[16–18]. Venous blood was taken for studies of neutrophil function, for total and differential white cell counts and arterialized capillary blood for oxygen tension. Within 6–8 h of the start of the operation and after return to an intensive care unit, a repeat double isotope study was performed and arterial oxygen tension was measured. Arterial blood was taken from an indwelling cannula for neutrophil degranulation studies which, in this laboratory, have shown no arteriovenous differences for neutrophil counts or degranulation products. Differential white cell counts were repeated. A third double isotope study was performed 24 h after the second study and between 28 and 48 h after start of surgery. All other determinations were repeated at 24 and 48 h.

Determination of transferrin accumulation

Circulating erythrocytes and transferrin were labelled *in vivo* with ^{99m}technetium (^{99m}Tc) and ^{113m}indium (^{113m}In) respectively[18]. After injection of ^{113m}In and 2 ml stannous pyrophosphate to prepare erythrocytes for ^{99m}Tc labelling, a single, mobile, collimated sodium iodide detector was positioned in turn for 1 min over the upper lobe of each lung anteriorly, and over the heart, with the patient supine. The ^{113m}In counts simultaneously recorded in the ^{99m}Tc channel were used as a cross channel correction factor and stored on an on-line BBC microcomputer which handled all data collected. Accurate repositioning of the detector was ensured using three lights attached to the detector head which could be focused onto marks on the patient's skin. Twenty minutes after the ^{113m}In (20 MBq) injection, ^{99m}Tc (12 MBq) was injected intravenously and a 1-h counting period began after a further 20 min. Simultaneous counts from each isotope were collected for 30 s at each of the three sites. ^{99m}Tc counts were corrected by the computer using the cross channel correction factor. The ratio of indium lung counts: indium heart counts was divided by technetium lung counts: technetium heart counts and plotted against time. A best fit regression line through the data was calculated. The protein accumulation index was numerically equal to the gradient of this line and has units of 10^{-3}/min[18–20].

Systemic oxygenation was expressed as the $P_{a,O_2}/F_{I,O_2}$ ratio derived from circulating oxygen tension (kPa) and the inspired oxygen fraction (per cent × 10^{-2}) which was determined by oxygen fuel cell electrodes

Neutrophil degranulation studies

Plasma was separated from venous or arterial samples collected in polypropylene tubes containing disodium EDTA (3.4 mmol/l final concentration) and kept on melting ice. All blood samples were centrifuged within 10 min of collection at 400 *g* for 10 min at 4°C and plasma stored at −20°C until assayed in batches. Serum samples were handled similarly but without EDTA. Two primary granule products (β-glucuronidase and elastase) and one secondary granule product (lactoferrin) were studied. Lactoferrin was determined by an enzyme-linked immunosorbent assay (ELISA). A standard curve was prepared for each assay and intra- and interassay variation were 6.2 per cent and

0007–1323/88/090883–04$3.00

12·0 per cent respectively. β-Glucuronidase activity was determined spectrophotometrically[19].

Release of neutrophil elastase was quantified by determination of an α_1-antitrypsin–elastase complex (elastase complex) using a locally developed ELISA with intra- and interassay coefficients of variation of 6·7 per cent and 12 per cent respectively. Free elastase activity in broncho-alveolar lavage fluid was determined spectrophotometrically[20]. Total and differential white cell counts and platelet counts were performed on a Technicon H6000 Coulter counter (Technicon Instruments and Company Ltd., Basingstoke, UK).

Broncho-alveolar lavage

Within 8 h of start of surgery the lung on the thoracotomy side was lavaged. Patients were ventilated and sedated and after pre-oxygenation (F_{I,O_2}, 1·0) 2–4 ml of 4 per cent lignocaine was injected via the endotracheal tube. Physiological saline at 37°C was used in 3 × 20 ml boluses. The aspirate from the first bolus was discarded and further aspirates were collected after each bolus into a trap at 4°C. No correction was made for dilution.

Statistical analysis

Data are given throughout as mean with standard deviation in parentheses. The significance of changes was assessed by an analysis of variance on a repeated measures design (ANOVA) or by a Student's *t* test (paired data) when comparing results on two occasions only. Significance was accepted where $P < 0·05$.

Results

Pre-operative protein accumulation indices for the collapsed and dependent lung were 0·28 (0·32) and 0·27 (0·26) respectively. The PAI increased significantly in both lungs at 8 h after surgery (*Figure 1*). The protein accumulation index rose on the thoracotomy side to 1·53 (0·51), $P < 0·001$, and on the dependent side to 0·85 (0·82), $P = 0·031$. At the third study the mean protein accumulation index had fallen to 0·68 (0·93) and 0·62 (1·30) respectively.

Systemic oxygenation fell progressively ($P = 0·003$, ANOVA) from a pre-operative mean of 51·0 (7·64) to 29·67 (6·61) at 48 h. The fall at 8 h was not significant ($P = 0·06$, *Figure 2a*).

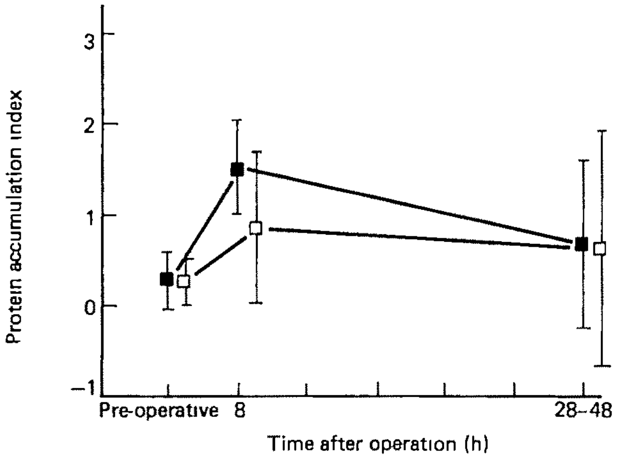


Figure 1 *The effect of oesophagectomy on the protein accumulation index (protein accumulation index × 10^{-3}/min) for the collapsed (■) and the dependent (□) lung. Data are mean (s.d.)* $P < 0·05$ *(pre-operative* versus *8 h) for both lungs*

Plasma lactoferrin and elastase complex concentrations rose significantly above baseline at 8 h ($P = 0·013$, $P = 0·005$, *Figure 2b*). Whereas the peripheral neutrophil count continued to rise throughout the study period ($P = 0·005$, ANOVA, *Table 1*), lactoferrin levels and elastase complex concentrations fell again between 8 and 48 h. The β-glucuronidase activity did not vary significantly ($P = 0·93$, ANOVA) from the pre-operative mean of 27·12 (16·24) throughout the study period (data not shown).

In the broncho-alveolar lavage fluid, elastase complex was detected in 8 of 9 patients and concentrations were higher than in the paired 8 h plasma sample in four patients. No free elastase activity was detected.

Peripheral platelet, lymphocyte and eosinophil counts fell significantly with time ($P = 0·024$, $P < 0·001$, $P = 0·016$ respectively, ANOVA, *Table 1*). Widespread bilateral radiographic infiltrates were evident in 8 of 9 patients postoperatively.

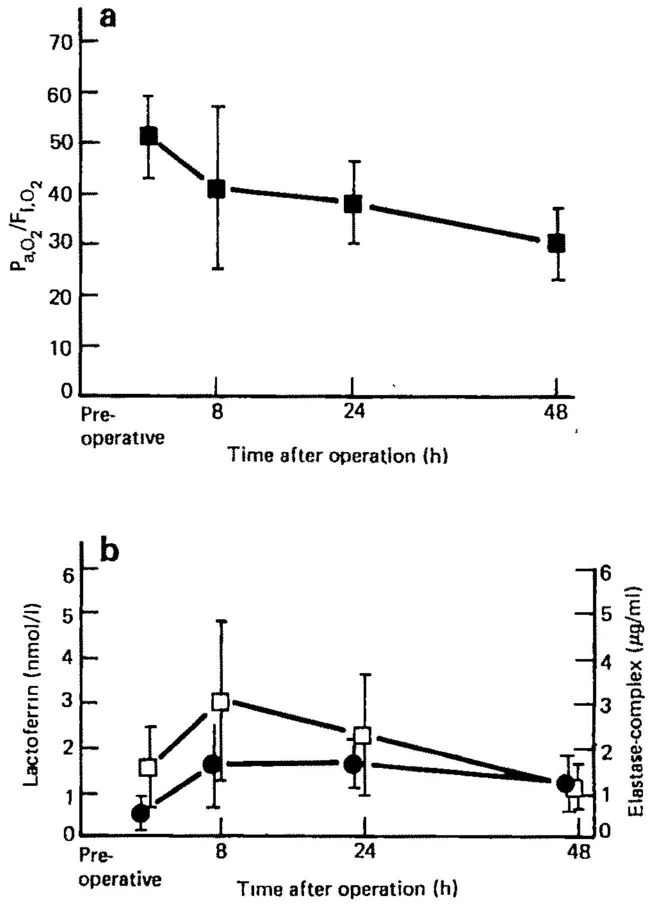


Figure 2 **a** *The effect of oesophagectomy on oxygenation expressed as the P_{a,O_2} · F_{I,O_2} ratio (kPa/per cent $O_2 \times 10^{-2}$),* $P = 0·003$ *(ANOVA).* **b** *The effect of oesophagectomy on plasma lactoferrin (□) and elastase complex (●) concentrations* $P < 0·05$ *(pre-operative* versus *8 h) for both parameters*

Table 1 *The effect of oesophagectomy on circulating absolute platelet, neutrophil, lymphocyte and eosinophil counts (× 10^6/ml)*

		Time after operation		
	Pre-operative	8 h	24 h	48 h
Platelets*	291 (64)	241 (71)	215 (34)	207 (61)
Neutrophils*	4·61 (1·73)	9·30 (3·08)	9·91 (6·66)	10·61 (2·72)
Lymphocytes*	1·66 (0·87)	0·54 (0·16)	0·72 (0·20)	0·78 (0·21)
Eosinophils*	0·17 (0·13)	0·02 (0·01)	0·01 (0·01)	0·13 (0·17)

* $P < 0·05$ (ANOVA by repeated measurement design)

Discussion

Neutrophil degranulation, increased lung capillary permeability to transferrin and bilateral radiographic infiltrates were consistent findings following oesophagectomy. Such features occur in animal models of ARDS and in the established state in man[5,6,9,16–18,21,26]. In patients following surgery, however, the mild transient inflammatory response does not usually progress to clinically significant lung injury and ARDS probably represents a qualitatively similar, but more severe and protracted, response[22,23]. The main advantage of studying patients after major surgery is the ease of relating inflammatory changes to a specific event.

We chose to study patients undergoing oesophagectomy where lung injury due to handling, collapse and re-expansion on the thoracotomy side would be more severe than that sustained by the dependent lung. The changes in transferrin accumulation were more marked on the thoracotomy side and confidence in accepting as genuine the transient postoperative increases in permeability was increased by the similar pre- and late postoperative values for each lung. The double isotope method has been reported to be sensitive and specific for increased pulmonary microvascular permeability to protein in the dog[21], and in man it was sensitive enough to detect transferrin accumulation in normal subjects as well as in those with ARDS[16–18]. The double isotope method might have a role in the early detection of direct or indirect lung injury, but it is not specific for established ARDS as currently defined[24,25].

The increase in the protein accumulation index, which reached levels reported in ARDS on the directly injured side[16–18], the fall in oxygenation at 8 h and peak circulating levels of lactoferrin and elastase complex concurred. An association between neutrophil activation and increased pulmonary permeability was reported in dogs following cardiopulmonary bypass[25], and in animal models of ARDS there is evidence for neutrophil involvement in the development of microvascular injury[8–10]. In the study reported here, however, no patient developed ARDS despite a doubling of lactoferrin levels, an increase greater than that reported in established ARDS[26], although the role of lactoferrin in lung injury is uncertain. Evidence of neutrophil degranulation following surgery reduces the value of monitoring granule products in patients at risk of ARDS, since degranulation is not a specific marker of development of the disorder[27]. The transient rise in lactoferrin concentration was markedly different from changes in other secondary granule products (cobalamin binding protein and lysozyme) reported after hysterectomy, where serum levels increased for up to 5 days[27]. Whether this reflects differential release or clearance is uncertain.

There are few available data in man concerning intravascular elastase release. The increase in elastase complex in this study was of a similar magnitude to increases reported after abdominal surgery[28]. Endothelial cells are damaged by elastase[29,30], which might be involved in the mechanism of both direct and indirect lung injury. Intrapulmonary elastase release was evident from the detection of elastase complex in bronchoalveolar lavage fluid, but since no free elastase activity was detected it is probable that intra-alveolar antiproteinase capacity was not exceeded.

The significant reduction in lymphocyte and eosinophil counts after surgery may be related to the postoperative rise in endogenous corticosteroid levels. An alternative explanation for the eosinophil count, however, is the possibility of sequestration within pulmonary capillaries as part of the inflammatory response, as reported in ARDS[31].

It is becoming accepted that ARDS, as currently defined, may represent only the extreme end of a spectrum of respiratory dysfunction following injury, and that study of less severe examples of respiratory compromise may improve understanding of underlying pathophysiological mechanisms and lead to more effective treatment[22,23]. In this study there was evidence of a systemic inflammatory response with neutrophil degranulation and a bilateral increase in pulmonary microvascular permeability to transferrin. Changes occurring in the postoperative state in man may be mediated by mechanisms capable of initiating more severe lung injury. The study of such patients might increase understanding of the initiation and control of inflammatory processes which may lead to ARDS.

Acknowledgements

We are grateful to Mr W. E. Morgan and Mr F. D. Salama for permission to study their patients and to the operating theatre and intensive care unit staff of the City Hospital, Nottingham. This work was supported by awards from the Chest, Heart and Stroke Association and the Trent Region Health Authority to Dr D. J. Shale.

References

1 Gelb AF, Klein E. Hemodynamic and alveolar protein studies in noncardiac pulmonary edema. *Am Rev Respir Dis* 1976; **114**: 831–5.

2. Holter JF, Weiland JE, Pacht ER, Gadek JE, Davies WB. Protein permeability in the adult respiratory distress syndrome *J Clin Invest* 1986; **78**. 1513–21.

3. Zimmerman GA, Renzetti AD, Hill HR. Functional and metabolic activity of granulocytes from patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1983; **127**. 290–300.

4. Zimmerman GA, Renzetti AD, Hill HR. Granulocyte adherence in pulmonary and systemic arterial blood samples from patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1984; **129**: 798–804.

5. Weiland JE, Davis WB, Holter JF, Mohammed JR, Dorinsky PM, Gadek JE. Lung neutrophils in the adult respiratory distress syndrome. Clinical and pathophysiological significance. *Am Rev Respir Dis* 1986, **133**: 218–25

6. Worthen GS, Haslett C, Rees AJ, Gumbay RS, Henson JE, Henson PM. Neutrophil-mediated pulmonary vascular injury. Synergistic effect of trace amounts of lipopolysaccharide and neutrophil stimuli on vascular permeability and neutrophil sequestration in the lung *Am Rev Respir Dis* 1987; **136**: 19–28.

7. Haslett C, Worthen GS, Giclas PC, Morrison DC, Henson JE, Henson PM. The pulmonary vascular sequestration of neutrophils in endotoxemia is initiated by an effect of endotoxin on the neutrophil in the rabbit. *Am Rev Respir Dis* 1987; **136**; 9–18.

8. Heflin AC, Brigham KL. Prevention by granulocyte depletion of increased vascular permeability of sheep lung following endotoxemia. *J Clin Invest* 1981; **68**: 1253–60.

9. Tahamont MV, Malik AB. Granulocytes mediate the increase in pulmonary vascular permeability after thrombin embolism. *J Appl Physiol* 1983; **54**. 1489–95.

10. Judges D, Sharkey P, Cheung H *et al*. Pulmonary microvascular fluid flux in a large animal model of sepsis evidence for increased pulmonary endothelial permeability accompanying surgically induced peritonitis in the sheep. *Surgery* 1986; **99**: 222–33.

11. Maunder RJ, Hackmann RC, Riff E, Albert RK, Springmeyer SC. Occurrence of the adult respiratory distress syndrome in neutropenic patients. *Am Rev Respir Dis* 1986; **133**: 313–6.

12. Ognibene FP, Martin SE, Parker MM *et al* Adult respiratory distress syndrome in patients with severe neutropenia. *N Engl J Med* 1986; **315**: 547–51.

13. Fowler AA, Hamman RF, Good JT *et al* Adult respiratory distress syndrome: risk with common predispositions *Ann Intern Med* 1983; **98**: 593–7.

14. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ Clinical predictors of the adult respiratory distress syndrome *Am J Surg* 1982; **144**: 124–30

15. Neely WA, Robinson WT, McCullan MH, Bobo WO, Meadows DL, Hardy JD. Postoperative respiratory insufficiency: physiological studies with therapeutic implications *Ann Surg* 1970; **171**: 679–85.

16. Basran GS, Byrne AJ, Hardy JG. A noninvasive technique for monitoring lung vascular permeability in man. *Nucl Med Commun* 1985; **3**: 3–10.

17. Braude S, Nolop KB, Hughes JMB, Barnes PJ, Royston D. Comparison of lung vascular and epithelial permeability indices in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1986; **133**: 1002–5.

18 Rocker GM, Morgan AG, Pearson D, Basran GS, Shale DJ

Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure *Thorax* 1987; **42**: 620–3.

19. Fishman WH, Kato K, Antiss CL, Green S. Human serum β-glucuronidase and some of its properties. *Clin Chim Acta* 1967; **15**. 435–47
20. Kramps JA, Van Twisk CH, Van Der Linden AC L-pyroglutamyl-L-prolyl-L-valine-*p*-nitroanilide, a highly specific substrate for granulocyte elastase. *Scand J Clin Lab Invest* 1983; **43**. 427–32.
21. Dauber IM, Pluss WT, Van Grondelle A, Trow RS, Weil JV Specificity and sensitivity of noninvasive measurment of pulmonary vascular protein leak *J Appl Physiol* 1985; **59**. 564–74.
22. Rinaldo JE The prognosis of the adult respiratory distress syndrome. Inappropriate pessimism? *Chest* 1986; **90**· 470–1
23. Shale DJ The adult respiratory distress syndrome – 20 years on. *Thorax* 1987; **42**: 641–5.
24. Rocker GM, Pearson D, Stephens M, Shale DJ. An assessment of a double isotope method for the detection of transferrin accumulation in the lungs of patients with widespread pulmonary infiltrates. *Clin Sci* 1988; **75**: 47–52.
25. Braude S, Nolop KB, Fleming JS. Krausz T, Taylor KM, Royston D Increased pulmonary transvascular protein flux after canine cardiopulmonary bypass. Association with lung neutrophil sequestration and tissue peroxidation. *Am Rev Respir Dis* 1986, **134**. 867–72.
26. Hallgren R, Borg T, Venge P, Modig J. Signs of neutrophil and eosinophil activation in adult respiratory distress syndrome. *Crit Care Med* 1984, **12**: 14–18.
27. Davies JM, Sheppard K, Fletcher J. The effects of surgery on the activity of neutrophil granule proteins. *Br J Haem* 1983; **53**: 5–13.
28. Duswald K-H, Jochum M, Schramm W, Fritz H Released granulocyte elastase. an indicator of pathobiochemical alterations in septicemia after abdominal surgery. *Surgery* 1985, **98**: 892–9.
29. Harlan JM, Killen PD, Harker LA, Striker GE, Wright DG Neutrophil-mediated endothelial injury *in vitro* Mechanisms of cell detachment *J Clin Invest* 1981, **68**. 1394–1403.
30. Smedley LA, Tonnesen MG, Sandhaus RA *et al.* Neutrophil-mediated endothelial injury. Enhancement by endotoxin and essential role of neutrophil elastase *J Clin Invest* 1986; **77**· 1233–43
31. Hallgen R, Samuelsson T, Venge P, Modig J. Eosinophil activation in the lung is related to lung damage in adult respiratory distress syndrome. *Am Rev Respir Dis* 1987, **135**: 639–42

Paper accepted 25 May 1988

Surgical workshop

Br. J. Surg. 1988, Vol. 75, September, 886–887

Left gastric venous caval shunt with externally reinforced polytetrafluoroethylene graft

J. Kambayashi, Y. Tsuji*, M. Danno*, T. Ohshiro and T. Mori

*The Second Department of Surgery, Osaka University Medical School and *The Department of Surgery, Tennouji Hospital, Osaka, Japan*

Correspondence to: Dr J. Kambayashi, The Second Department of Surgery, Osaka University Medical School, 1-1-50 Fukushima, Fujushima-ku, Osaka 553, Japan

In 1968, Inokuchi[1] proposed left gastric venous caval shunt (LGCS) as an ideal selective shunt procedure for the treatment of portal hypertension: LGCS was intended to assure postoperative portal perfusion and to prevent Eck's syndrome. Although excellent results with this procedure have been documented[2], it has not yet gained global popularity because of its technical difficulties including the lack of a suitable autogenous vein graft. Recently, we have successfully treated a patient with recurrent variceal haemorrhage by LGCS, utilizing an externally reinforced (ringed) expanded polytetrafluoroethylene (EPTFE) vascular prosthesis. The clinical result is excellent and the patency of the shunt has been confirmed.

Patient and methods

Case presentation

A 57-year-old woman, who had been suffering from oesophageal varices due to idiopathic portal hypertension, experienced two episodes of haematemesis and subsequent melaena in February 1987 and she was then admitted to our service Physical examination revealed no abnormalities except marked splenomegaly. She received 1400 ml of transfusion together with plasma for the first 3 days. Even after the transfusion, leucopenia and thrombocytopenia were present. All other laboratory tests were within normal values. Endoscopic examination and fluorography revealed the presence of advanced oesophageal varices with a positive red colour sign. Abdominal ultrasonography disclosed a markedly enlarged vein near the angle of stomach, which was thought to be either the left gastric vein or splenic vein. After she had fully recovered from anaemia and general fatigue, surgical treatment was considered for the prevention of further variceal bleeding. Considering her age, relatively good risk and the presence of hypersplenism, LGCS and splenectomy were planned

Operative procedure

The abdomen was entered through a transverse incision and no ascites was found On careful inspection, a markedly dilated (about 15 mm diameter) tortuous left gastric vein was noted. No such venous dilatation was observed in either the short gastric or the mesenteric venous system. A catheter was introduced into the portal vein via a branch of the superior mesenteric vein to monitor portal venous pressure and the initial value was 38 cmH$_2$O. The splenic pulp pressure was exactly the same as the portal pressure. Consequently, it was considered that the left gastric vein and its branches were the principal portal collateral system causing advanced oesophageal varices First, splenectomy was performed; the resected specimen weighed 730 g. The portal pressure after splenectomy was 33 cmH$_2$O The lesser sac was then entered and the left gastric vein was dissected and encircled with a tape The duodenum was mobilized by Kocher's manoeuvre and the inferior vena cava was exposed but the proximal portion was adherent to the caudate lobe of the liver, as illustrated in *Figure 1* Under systemic heparinization (3000 units IV bolus), the vena cava was partially occluded by a Satinsky clamp just below the renal veins and the anastomotic orifice was created Then, a ringed EPTFE graft (12 mm in diameter, Japan GORE-TEX*) was anastomosed to the vena cava, end-to-side, with continuous 5-0 EPTFE sutures. The other end of the graft was placed near the isolated left gastric vein via the foramen of Winslow Then the proximal anastomosis was performed in an end-to-end fashion, using the same sutures. Releasing the clamp and the tape, the LGCS was completed as illustrated in *Figure 1*, the total length of the graft used was 11 cm. The portal pressure after the completion of the shunt was 38 cmH$_2$O, which was the same as the initial value.

---

* GORE-TEX is a trademark of W L Gore and Associates, Inc.

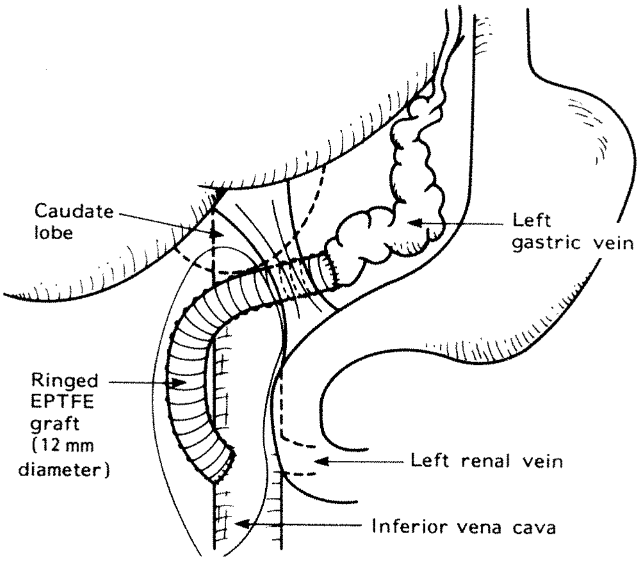


Figure 1 *Diagrammatic representation of the left gastric venous caval shunt, using an externally reinforced EPTFE graft*

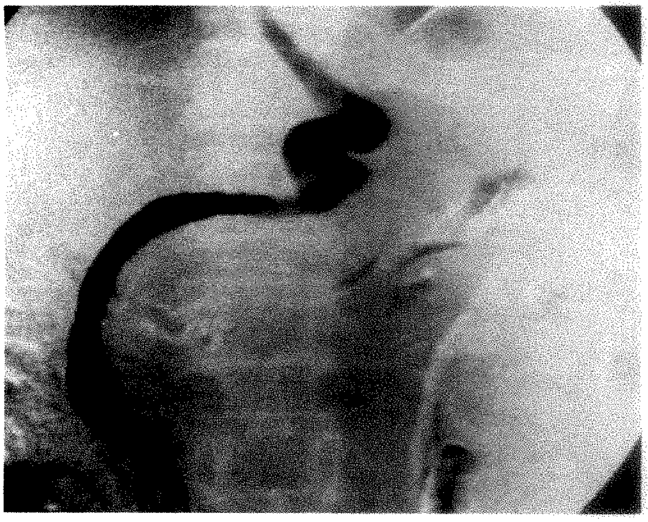


Figure 2 *Digital subtraction venography, demonstrating the patency of the graft. A catheter was introduced into the anastomotic orifice from the inferior vena cava by femoral vein puncture*

Results

The patient made an uneventful recovery except for the occasional low-grade fever and left pleural effusion; she was discharged on the 55th postoperative day in excellent condition. On the 24th postoperative day, endoscopic examination of the oesophagus was performed, which disclosed a marked reduction in the size of the varices. This was further confirmed by upper gastrointestinal X-ray examination on the 45th postoperative day, which showed a reduction in the size of the varices compared with the pre-operative study. The patient was placed on warfarin (4 mg/day) after oral intake was initiated to maintain the patency of the shunt. Histological examination of the liver revealed the presence of degeneration and fibrosis, which is compatible with the pre-operative diagnosis. Three months after discharge, retrograde venography was performed to confirm the patency and to monitor the shunt pressure. As shown in *Figure 2*, the patency was confirmed; the pressure inside the graft and the vena cava was 10·5 and 10·0 cmH_2O, respectively. The patient is well and has not experienced any gastrointestinal tract symptoms.

Discussion

In the field of portal-systemic shunt operations, vascular prostheses have already been applied to mesocaval shunts[3] and distal splenorenal shunts[4]. This paper describes the first application of a prosthesis in LGCS. The favourable results can be attributed to the use of the externally reinforced (ringed) graft which is resistant against kinking, thus avoiding compression of the graft by the hepatoduodenal ligament due to the relatively loosely attached left gastric vein. In the original method of LGCS[5], autogenous vein graft was used for the interposition. In our case, the diameter of the left gastric vein was so large that it would be impossible to use an autogenous vein graft. The general disadvantages to the use of a prosthesis include graft occlusion and infection, which may be prevented by the use of anticoagulant and chemotherapy. In this patient, the graft was longer than is ideal because the caudate lobe was adherent to the proximal portion of the vena cava. Our experience suggests that LGCS, an excellent selective shunt, may be safely performed without technical difficulties by the use of externally reinforced vascular prosthesis.

References

1. Inokuchi K. A selective portocaval shunt. *Lancet* 1968; **ii**: 51–2.
2. Inokuchi K, Beppu K, Koyanagi N, Nagamine K, Hashizume M, Iwanaga T, Sugimachi K. Fifteen years' experience with left gastric venous caval shunt for esophageal varices. *World J Surg* 1984; **8**: 716–21.
3. Lord JW, Rossi G, Daliana M, Rosati LM. Mesocaval shunt modified by the use of a Teflon prosthesis. *Surg Gynecol Obstet* 1970; **130**: 525–8.
4. Nagasue N, Ogawa Y, Yukaya H, Hirose S. Modified distal splenorenal shunt with expanded polytetrafluoroethylene interposition. *Surgery* 1985, **98**: 870–7.
5. Inokuchi K, Kobayashi M, Kusaba A, Ogawa Y, Saku M. New selective decompression of esophageal varices by a left gastric venous-caval shunt. *Arch Surg* 1970; **100**: 157–60.

Paper accepted 27 March 1988

Br. J. Surg. 1988, Vol. 75, September, 888–891

Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis

**D. Bergqvist,
T. Mätzsch,
U. S. Burmark*,
J. Frisell†, O. Guilbaud*,
T. Hallböök‡, A. Horn§,
A. Lindhagen‡,
H. Ljungnér¶,
K.-G. Ljungström∥,
H. Onarheim§, B. Risberg**,
S. Törngren† and
P. Örtenwall****

*Departments of Surgery, General Hospital, Malmö, †Södersjukhuset, Stockholm; ‡Kärnsjukhuset, Skövde; ¶Länssjukhuset, Halmstad; ∥Danderyd's Hospital; ** Östra sjukhuset, Gothenburg; *KabiVitrum, Stockholm, Sweden; and §Haukeland Hospital, Bergen, Norway*

Correspondence to:
Dr D. Bergqvist, Department of Surgery, General Hospital, S-214 01 Malmö, Sweden

A prospective randomized double-blind trial was performed comparing conventional low-dose heparin with a low molecular weight heparin fragment for thromboprophylaxis in elective general abdominal surgical patients. The first dose of the heparin fragment was given the evening before surgery, and further doses were given thereafter every evening. There were 1002 analysable patients, 826 having received correct prophylaxis. Of these 1002 patients, 64 per cent were operated on for malignant disease. A total of 20 patients died, 10 in each group. The 5·0 per cent, P = 0·02). The frequency of bleeding was 6·7 per cent among patients with correct prophylaxis with the heparin fragment (9·2–5·0 per cent, P = 0·02). The frequency of bleeding was 6·7 per cent among the heparin fragment patients and 2·7 per cent among the patients given conventional heparin (P = 0·01), but all bleeds were of minor degree and there was no difference in the reoperation rate for bleeding, or in the transfusion requirements. Local pain at the injection site was reported significantly less often among patients given the heparin fragment.

Keywords: Low molecular weight heparin, low dose heparin, postoperative thrombo-embolism, prophylaxis

The recently developed low molecular weight heparins (LMWH) constitute a promising alternative form of prophylaxis against postoperative deep vein thrombosis (DVT). A good thromboprophylactic effect has been shown[1–5], though there have also been some reports of haemorrhagic side-effects[1,3,6]. There are three main problems concerning the use of various LMWH preparations. The first is that differences in preparation procedures and in molecular weight result in differences in pharmacokinetics and pharmacodynamics. The second is the lack of uniformity in definitions of activity and in the evaluation of effects[7,8]. The third problem concerns the inadequacy of our knowledge of optimal dosage and intervals between doses.

In a previous study of patients undergoing elective general abdominal surgery, in which the effects of LMWH at a dosage of 5000 XaI activity units given once daily were compared with those of conventional low-dose heparin given twice daily, the frequency of postoperative DVT was comparable in both groups. There were, however, more bleeding complications in the LMWH group[3]. As recent pharmacokinetic studies have shown, the appearance of bleeding complications coincides with maximum factor Xa inhibition[9–13]. In planning the present study it was therefore considered logical to use the same dose as in the previous study, but to prolong the interval between the first dose and surgery.

The aim of this study was to compare the thromboprophylactic effect and bleeding side-effects of LMWH in the dose of 5000 XaI units once daily, giving the first dose the evening before surgery and the next the evening after surgery, with conventional low-dose heparin given twice daily starting 2 h before surgery.

Patients and methods

Study design

The study was designed as a prospective, randomized, double-blind multicentre trial. Between 18 February 1985 and 31 March 1987, patients scheduled for elective general abdominal surgery at seven centres were randomly assigned to LMWH or low-dose heparin treatment. In all, 1040 patients were randomized.

(1) *Inclusion criteria.* Patients were 40 years of age or older and scheduled to undergo major elective general abdominal surgery of more than 30 min duration and with an expected postoperative stay in hospital of at least 5 days.
(2) *Exclusion criteria.* Vascular and urogenital surgery; heparin or iodine hypersensitivity; impaired renal function (creatinine > 200 μmol/l); septic endocarditis; haemorrhagic stroke; known bleeding diathesis; treatment with oral anticoagulants or dextran within 14 days; pregnancy.

At each centre randomization was done in blocks of 10 consecutive patients, the block size being unknown to the investigators. After randomization, 38 patients were excluded; 27 because of cancelled operations, 4 owing to withdrawal of consent after randomization but before the first injection, and 7 for various other reasons, leaving 1002 patients for analysis.

The study groups were well matched (*Table 1*). *Table 2* shows the types of surgery and the number of patients operated on for malignant diseases, malignancy being the indication in 63·6 per cent. There were no significant differences between the groups in *Tables 1* and *2*. Epidural block in addition to the general anaesthesia was administered to 20 per cent of the LMWH patients and 22 per cent of the low-dose heparin patients.

Heparins

The low molecular weight heparin fragment (Fragmin®, Kabi 2165,

0007-1323/88/090888-04$3.00 © 1988 Butterworth & Co (Publishers) Ltd

Table 1 *Comparison of risk factors*

	LMWH	Low-dose heparin
Age (years)*	68 (41–91)	69 (41–91)
Sex (male/female)	246/259	242/255
Broca's index*†	0·98 (0·63–1·7)	0·99 (0·63–1·7)
Pre-operative hospitalization time (days)*	3 (1–94)	3 (1–56)
Duration of surgery (min)*	120 (25–460)	125 (15–474)
Previous myocardial infarction	30 (5·9)	39 (7·8)
Previous venous thrombo-embolism	37 (7·3)	30 (6·0)
Previous major orthopaedic event	58 (11·5)	62 (12·5)
Previous malignancy‡	82 (16·2)	88 (17·7)
Varicose veins	109 (21·6)	102 (20·5)
Leg ulceration	2 (0·4)	1 (0·2)

Figures in parentheses represent range or percentage; *median and range; †weight (kg)/height (cm) − 100; ‡excluding the present indications of surgery which are shown in *Table 2*. LMWH, low molecular weight heparin

KabiVitrum AB, Stockholm, Sweden) was prepared from pig mucosal sodium heparin by partial degradation with nitrous acid. The average molecular weight was approximately 5000 with 80 per cent of the molecules between 3000 and 8000. As compared with the 4th International Standard for heparin (NIBSC), the specific anticoagulant activity was 160 units/mg when measured with an amidolytic anti-factor Xa assay (plasma S-2222), and 40 units/mg when measured with an APTT assay. The corresponding figures were 160 units/mg and 60 units/mg when assayed against the 1st International Standard for low-molecular-weight heparin. The fragment was supplied in single-dose syringes containing 5000 XaI activity units (30 mg heparin) per 0·2 ml.

Conventional sodium heparin of pig mucosal origin was supplied in identical single-dose syringes of 5000 units/0·2 ml (=XaI activity).

Prophylactic regimen

The patients were given their first injection subcutaneously at 10 p.m. on the evening of the day before surgery, and the second injection 2 h before surgery. The following injections were given at 12-h intervals for 5–8 days. Injections were given subcutaneously in the lateral aspect of the thigh (at one centre) or in the abdominal wall (at the other six).

(1) *Heparin fragment*. Syringes with uneven numbers contained 5000 units (XaI activity) of Kabi 2165 and syringes with even numbers contained placebo. The patients thus received heparin fragment every evening starting the day before surgery, and placebo in the mornings.
(2) *Conventional low-dose heparin*. The first syringe contained placebo and all the following 5000 units heparin.

Correct prophylaxis was defined as the administration of both pre-operative injections and a total of at least 11 injections (including the pre-operative) in correct sequence or until a thrombo-embolic or haemorrhagic end-point was reached or death occurred.

Diagnostic procedures

Screening for postoperative deep vein thrombosis was done for 7 days with the ^{125}I-labelled fibrinogen uptake test (FUT; 100 μCi (3·7 MBq) fibrinogen (Amersham, UK)). The fibrinogen was given on the day before surgery. Measurements were made once pre-operatively, and then for seven postoperative days. An increase in uptake of 20 per cent or more between two adjacent points in the same leg, or between the same points in the two legs, was considered diagnostic of DVT if it persisted for at least 24 h. Patients with positive FUT underwent phlebography whenever possible, all negative phlebograms being scrutinized by the same independent radiologist. All patients were followed up on the 30th postoperative day to record any clinical complications or mortality.

The recording of complications

Intra-operative bleeding was estimated from swabs and suction bottles by the anaesthetist. This is the standard clinical way of assessing bleeding and considered adequate in a double-blind trial. Transfusion requirements were recorded. All instances of postoperative bleeding, wound haematoma and reoperation were recorded. Bleeding complications were classified in three categories:

(1) diffuse bleeding (i.e. probable haemostatic defect),
(2) surgical bleeding (i.e. arterial lesion, retractor injury to the spleen),
(3) haemorrhage unrelated to the operation (i.e. duodenal ulceration, intracerebral bleeding).

Wound infection and intra-abdominal abscesses, allergic side-effects, and local complications (haematoma, pain) at the injection site were recorded.

All cases of thrombo-embolic and haemorrhagic side-effects were discussed and agreed upon by all participating investigators before breaking the code.

Statistical methods

The determination of the number of patients required for the study was based on power considerations concerning the expected proportions of thrombosis in the two treatment groups. It was decided that, if one proportion of deep vein thrombosis was 0·05 and the other 0·10, the difference should be detectable with a power of at least 80 per cent using a two-sided test at a significance level of 5 per cent. This led to the requirement of an effective number of about 840 patients with correct prophylaxis.

Rank tests adapted to the multicentre situation have been used for comparison of the two treatment modes: the Mantel–Haenzel test for proportions[14] and a pooled version of the Wilcoxon two-sample test[15]. These tests take into account the fact that independent randomizations were carried out at each centre, and they are sensitive to common tendencies in the data from the various centres. The P values referred to in the text correspond to two-sided tests, and 'non-significance' represents a P value larger than 5 per cent. Missing values were taken into account in analysis only through a corresponding reduction of sample sizes.

Ethics

The study was approved by the Ethics Committee, University of Lund. The patients gave their informed consent to participate before entering the study.

Results

Thrombosis

Of the total 1002 patients 69 developed postoperative DVT according to the FUT, 28 in the LMWH group (5·5 per cent, 95 per cent confidence interval 3·7–8·0 per cent) and 41 in the low-dose heparin group (8·3 per cent, 95 per cent confidence limits 6·0–11·1 per cent) (P = 0·08). Correct prophylaxis was given to 82 per cent or 826 patients (405 low-dose heparin and 421 LMWH) and among these the frequency of DVT was 5·0 per cent (95 per cent confidence limits 3·1–7·5 per cent) in the LMWH group, and 9·2 per cent (95 per cent confidence limits 6·5–12·4 per cent) in the low-dose heparin group (P = 0·02). Twenty-eight patients had thrombi on the right side, 29 on the left, and 12 had bilateral thrombi (only one patient in the LMWH group). Of the thrombi, 73 per cent were located in the calf. The median interval between surgery and diagnosis was 4 days in both groups (range 0–8 days in the LMWH group and 0–7 in the low-dose heparin group).

Twenty patients, ten from each group, died within 30 days of surgery (16 with correct prophylaxis), giving an overall

Table 2 *Type of surgery and number of malignancies operated on*

	LMWH	Low-dose heparin
Total number of patients	505 (311)	497 (326)
Gastric surgery	53 (24)	50 (24)
Biliary tract surgery	43 (4)	43 (8)
Colonic surgery	299 (194)	268 (190)
Rectal surgery	80 (73)	96 (83)
Pancreatic surgery	12 (9)	12 (9)
Miscellaneous	18 (7)	28 (12)

Figures in parentheses are the number of malignant cases. LMWH, low molecular weight heparin

Table 3 *Percentage frequency of thrombo-embolic complications with 95 per cent confidence limits*

	LMWH	Low-dose heparin	*P* value
Total material	5·5 (3·7–8·0)	8·7 (6·4–11·6)	0·05
Correct prophylaxis	5·0 (3·1–7·5)	9·7 (7·0–13·0)	0·01

One fatal and four scintigraphic pulmonary emboli, two of which were negative for the fibrinogen uptake test (all in the low-dose heparin group). LMWH, low molecular weight heparin

Table 4 *Bleeding, transfusion and haemorrhagic side-effects in the whole series*

	LMWH (*n* = 505)	Low-dose heparin (*n* = 497)
Bleeding and transfusion		
Intra-operative bleeding (ml)	300 (0–3500)	300 (0–10 000)
No. of transfused patients	223 (44)	215 (43)
Transfusion (units) in transfused patients	2 (1–12)	2 (1–25)
Haemorrhagic side-effects		
Total number of haemorrhagic complications (No. of patients)	30 (5·9)	15 (3·0)*
Diffuse bleeding	25	10†
Surgical bleeding	4	4
Bleeding from extra-operative source	1	1

Figures are median (range in parentheses) or number of patients (percentage in parentheses). LMWH, low molecular weight heparin; **P* = 0·03, †*P* = 0·01 (LMWH *versus* low-dose heparin)

mortality rate of 2 per cent. Of the fatal cases, 13 were operated on for malignant disease. Autopsy was performed in 10 cases. No non-fatal pulmonary emboli or DVT were found at autopsy, but one fatal pulmonary embolism was found in the low-dose heparin group. In the low-dose heparin group, clinical signs of gross pulmonary embolism, verified by scintigraphy, were found in four cases, in two of which the FUT had been negative. There was no death from haemorrhage. The overall frequency of thrombo-embolic complications is shown in *Table 3*.

Bleeding complications

Intra-operative blood loss, transfusion requirements and haemorrhagic complications are shown in *Table 4*. The total frequency of patients with haemorrhagic complications was 5·9 per cent (95 per cent confidence limits 4·0–8·4 per cent) in the LMWH group and 3·0 per cent (95 per cent confidence limits 1·7–4·9 per cent) in the low-dose heparin group ($P = 0{\cdot}03$). If analysis is confined to patients given correct prophylaxis, the corresponding frequencies are 6·7 per cent (95 per cent confidence limits 4·5–9·5 per cent) and 2·7 per cent (95 per cent confidence limits 1·4–4·8 per cent) respectively ($P = 0{\cdot}01$). The diffuse bleedings were mostly wound haematomas without need for drainage. The haemorrhagic complications occurred on day 1·5 (median, range 0–12) in the LMWH group and on day 3 (median, range 0–18) in the low-dose heparin group. Haemoglobin, measured pre-operatively and on postoperative days 4–6, was (mean ± s.d.): 130 ± 16 g/l and 117 ± 14 g/l, respectively, in the LMWH group, and 130 ± 18 g/l and 119 ± 14 g/l, respectively, in the low-dose heparin group. The postoperative values are statistically different ($P = 0{\cdot}02$).

The first LMWH dose was given 12·7 h (median, range 9·4–18·4) before surgery, the low-dose heparin 2·3 h (median, range 0·2–9·3) before surgery. The elapsed time between first dose and surgery did not differ between patients with haemorrhagic complications and patients who developed DVT.

Postoperative infectious complications occurred in 65 patients in the LMWH group (12·9 per cent) and in 59 patients in the low-dose heparin group (11·9 per cent). Other miscellaneous complications are listed in *Table 5*.

Discussion

At present there seems to be little doubt about the effectiveness of LMWH given once daily[1–3,5] but owing to the risk of haemorrhagic complications[1,3,6], precision in assessing optimal dosage is important.

The study design was based on the results of a previous multicentre trial[3], where the effects of conventional low-dose heparin were compared with those of LMWH administered once daily, the first dose being given 2 h before surgery. As the frequency of haemorrhagic side-effects in the study was unacceptably high, a new study was designed where the first dose was to be administered the evening before surgery but still using 5000 XaI units once daily. There are two important differences between the studies: the mean age of patients was three years higher in the present study, and the frequency of malignant cases about 50 per cent higher. The present series is thus composed of patients with a higher risk of thrombo-embolic complications. This fact was reflected in a higher frequency of deep vein thrombosis in the present low-dose heparin group than in the previous one (9 *versus* 4 per cent). Despite the higher risk, LMWH was significantly more efficacious than low-dose heparin in preventing DVT. The frequency of DVT in the low-dose heparin group is what might be expected in a patient population of the type studied[2,4,16–22] The reduction in frequency of thrombosis in the LMWH group is in keeping with findings by Kakkar and Murray[2].

To obtain a large enough series within a reasonable time, the study was designed as a multicentre trial with all the difficulties inherent in such studies. By means of separate randomization at each centre, and weighting their data in the statistical analysis, such difficulties have been satisfactorily minimized. Background data and pre-operative risk factors showed the randomization to have been adequate, and the two groups to be fully comparable. Out of 1040 patients only 38 were excluded from analysis (3·7 per cent) compared, for instance, with the 15 per cent in a recent multicentre trial[21].

Owing to a higher frequency of diffuse bleeding there was significantly more bleeding in the LMWH group than in the conventional low-dose heparin group. The patients with diffuse bleeding did not receive their injection with a shorter interval until surgery, nor did they differ in body weight. The clinical significance of the bleeding was minor, and there was no increase in the frequency of reoperation (0·6 per cent), the need for transfusions or infectious complications. In a study where a thromboprophylactic effect of a drug with potential effect on haemostatic mechanisms is being evaluated, there is a tendency to over-report bleeding episodes which are of no clinical importance. This is an important argument for conducting only truly blind studies. Because of lack of uniformity in definitions,

Table 5 *Miscellaneous complications*

	LMWH	Low-dose heparin
Haematoma at injection site	36 (7·1)	47 (9·5)
Local pain	23 (4·6)	59 (11·9)*
Allergic reaction	0	0
Reoperation (non-haemorrhagic)	31 (6·1)	27 (5·4)
Others	10 (2·0)	6 (1·2)

Number of patients (percentage in parentheses). LMWH, low molecular weight heparin; **P* < 0·001 (LMWH *versus* low-dose heparin) comparing frequencies between various studies is difficult. None the less, the frequency of haemorrhagic side-effects found in the low-dose heparin group was very similar to that reported by Sasahara *et al.*[21], also from a double-blind trial. Our frequency of reoperation for haemorrhage of 0·6 per cent may be compared with 1·9 per cent in the low-dose heparin group in a Scandinavian–Swiss multicentre trial[23] where heparin was given three times daily[24]. One centre used heparin injections in the thigh, the other six in the abdominal wall, but there were no differences in frequency of thrombosis or bleeding complications related to the variation in injection site. Especially in gynaecological surgery, this may be of importance[2], but we had no such operations included.

This study introduces a new principle as far as heparin prophylaxis is concerned: giving the first dose of a heparin fragment in the evening before surgery. The prophylactic effect of LMWH was significantly better than that of conventional low-dose heparin, although in the LMWH group the interval between the first dose and surgery exceeded 10 h in most patients. The effect was not better in those patients where the interval was shorter, a finding with two important implications. One is practical: the simplicity of a prophylactic regimen that can be instituted at a fixed time the previous evening, when ward activity is low, regardless of the scheduled time for surgery the next day, and then repeated once every evening. The other implication is theoretical: is it possible to prolong the interval between injections even more than 24 h or to decrease the dose, including the pre-operative dose?

In conclusion, the advantages of using the LMWH fragment as outlined in this study compared with conventional low-dose heparin are simplified administration routines, better thromboprophylactic effect and less local pain at injection site. A disadvantage is the slight increase in haemorrhagic side-effects, even though the bleeding episodes were of minor clinical importance. Heparin fragment administered the evening before surgery and then every evening is a practically acceptable alternative way of preventing postoperative DVT in patients undergoing elective general abdominal surgery.

Acknowledgements

This study was supported by a grant from the Swedish Medical Research Council (No. 00759).

References

1. Schmitz-Huebner U, Bunte H, Freise G *et al.* Clinical efficacy of low molecular weight heparin in postoperative thrombosis prophylaxis. *Klin Wochenschr* 1984; **62**: 349–53.
2. Kakkar VV, Murray WJG. Efficacy and safety of low-molecular-weight heparin (CY 216) in preventing postoperative venous thrombo-embolism: a co-operative study. *Br J Surg* 1985; **72**: 786–91.
3. Bergqvist D, Burmark US, Frisell J *et al.* Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily: a prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg* 1986; **73**: 204–8.
4. Onarheim H, Lund T, Heimdal A, Arnesjö B. A low molecular weight heparin (Kabi 2165) for prophylaxis of postoperative deep venous thrombosis. *Acta Chir Scand* 1986; **152**: 493–596.
5. Turpie AGG, Levine MN, Hirsch J *et al.* A randomized controlled trial of a low molecular weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986; **315**: 925–9.
6. Koller M, Schoch U, Buchmann P, Largiader F, von Felten A, Frick PG. Low molecular weight heparin (Kabi 2165) as thromboprophylaxis in elective visceral surgery: a randomized, double-blind study versus unfractionated heparin. *Thromb Haemost* 1986; **56**: 243–6.
7. Barrowcliffe TW, Curtis AD, Tomlinson TP, Hubbard AR, Johnson EA, Thomas DP. Standardization of low molecular weight heparins: a collaborative study. *Thromb Haemost* 1985; **54**: 675–9.
8. Thomas DP, Barrowcliffe TW, Curtis AD. Low molecular weight heparin: a better drug? *Haemostasis* 1986; **16**: 87–92.
9. Bergqvist D, Hedner U, Sjörin E, Holmer E. Anticoagulant effects of two types of low molecular weight heparin administered subcutaneously. *Thromb Res* 1983; **32**: 381–91.
10. Bratt G, Tornebohm E, Widlund L, Lockner D. Low molecular weight heparin (Kabi 2165, Fragmin): pharmacokinetics after intravenous and subcutaneous administration in human volunteers. *Thromb Res* 1986; **42**: 613–20.
11. Dawes J, Prowse CV, Pepper DS. Heparin, LMW heparin and SP54 concentration after subcutaneous injection, assessed by competitive binding assay. *Thromb Res* 1986; **44**: 683–93.
12. Harenberg J, Zimmermann R, de Vries JX, Weber E. Gerinnungshemmung durch niedermolekulares Heparin. *Münch Med Wchschr* 1986; **128**: 541–2.
13. Mätzsch T, Bergqvist D, Hedner U, østergaard P. Effects of an enzymatically depolymerized heparin as compared with conventional heparin in healthy volunteers. *Thromb Haemost* 1987; **57**: 97–101.
14. Cochran WG. *Planning & Analysis of Observational Studies*. New York: Wiley, 1983: Section 6.3.
15. Lehmann EL. *Nonparametrics: Statistical Methods Based on Ranks*. San Francisco: Holden-Day, 1975: Section 3.3.
16. Bergqvist D, Hallbook T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. A study with the ^{125}I-fibrinogen test. *World J Surg* 1980; **4**: 239–43.
17. Gruber UF, Friedrich R, Duckert F, Torhorst J, Rem J. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. *Lancet* 1977; **i**: 207.
18. Groote Schuur Hospital Thromboembolus Study Group. Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients. Interim report of a prospective trial. *Br Med J* 1979; **1**: 1447.
19. A multi-unit controlled trial. Heparin versus dextran in the prevention of deep-vein thrombosis. *Lancet* 1974; **ii**: 118.
20. Törngren S, Forsberg K. Concentrated or diluted heparin prophylaxis of postoperative deep venous thrombosis. *Acta Chir Scand* 1978; **144**: 283.
21. Sasahara AA, DiSerio FJ *et al.* Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis. A multicenter trial. *JAMA* 1984; **22**: 2960–6.
22. Törngren S, Brücke P, Haller U *et al.* A randomized study of a semisynthetic heparin analogue and heparin in prophylaxis of deep vein thrombosis. *Br J Surg* 1984; **71**: 817–20.
23. Gruber UF, Saldeen T, Brokop T *et al.* Incidences of fatal postoperative pulmonary embolism with dextran 70 and low-dose heparin: an international multicentre study. *Br Med J* 1980; **280**: 69.
24. Bergqvist D. Prophylaxis of postoperative thromboembolic complications with low-dose heparin: an analysis of different administration intervals. *Acta Chir Scand* 1979; **145**: 7–14.

Paper accepted 31 May 1988

Br. J. Surg. 1988, Vol. 75, September,
892–895

Choledochal cyst: a 14-year surgical experience with 36 patients

K. C. Tan and
E. R. Howard

Department of Surgery (Firm 3),
King's College Hospital,
Denmark Hill, London SE5 9RS,
UK

Correspondence to:
Mr E. R. Howard

The presentation and management of 36 patients with cystic dilatation of the biliary tree seen over a 14-year period is reviewed. There were 28 females and 8 males, a ratio of 3·5:1. The classic triad of jaundice, pain and an abdominal mass was seen in only seven cases. Twelve patients suffered recurrent pancreatitis. There were three cases of variceal haemorrhage from portal hypertension secondary to biliary cirrhosis, and one case of biliary peritonitis from a ruptured cyst. Internal drainage (cystenterostomy) was performed in nine patients but five of these eventually needed cyst excision. Cysts have been excised primarily in the last 21 consecutive patients without mortality. Preliminary external drainage with T tubes was used before cyst resection in three patients who presented with complications of choledochal cysts. Cyst excision and hepaticojejunostomy is now the definitive treatment of choice.

Keywords: Choledochal cyst, pancreatitis, primary excision, cyst drainage

Cystic dilatation of the biliary tree was once considered a rare congenital anomaly, but more than 3000 cases have now been reported. Females predominate, with a female to male ratio of nearly 4:1. It is more common in Oriental races and interestingly about a third of case reports were from people of Japanese origin[1,2]. It remains a rare condition in Western countries where its incidence has been estimated to be between 1 in 100 000 and 1 in 150 000 live births[3]. Tsardakas and Robnett[4] found only one case in 26 000 admissions in a London hospital, whereas the hospital admission rate in Japan[5] is about 1 in 1000. Cases from Britain have been reported sporadically[6–9]. Early reports suggested that internal drainage (choledochocystenterostomy) was a satisfactory surgical treatment, but with longer follow-up it is clear that complications occur in up to 40 per cent of cases[10]. Later reports have confirmed the safety and low morbidity of radical cyst excision[11] which is now recommended as primary treatment.

Patients and methods

Thirty-six patients with choledochal cyst were managed from 1973 to 1988 by one surgeon (E.R.H.). There were 28 females and 9 males, a ratio of 3·5:1. Twenty-nine of the patients were British. Of the 36 patients, 29 presented as new cases while 7 were referred for complications after previous surgery. The ages at the time of presentation ranged from birth to 51 years. Twenty-nine (81 per cent) were below 10 years of age and there were 13 infants (36 per cent) under 12 months of age.

The classic triad of jaundice, pain and a palpable abdominal mass was seen in only 7 (24 per cent) of the 29 presenting as new cases. Jaundice was the most common finding and occurred in 23 patients (79 per cent). It was intermittent in 18 patients. Pain was noted in 16 patients (55 per cent) and an abdominal mass was palpable in 9 (31 per cent).

Unusual presentations in three patients included a diagnostic ultrasound scan at 17 weeks gestation in a female fetus, peritonitis in a 7-month-old girl from spontaneous cyst rupture, and symptoms and signs of cholecystitis in a woman who was 10 weeks pregnant. Her symptoms progressed and the choledochal cyst was diagnosed after the onset of obstructive jaundice. Twelve of the patients with recurrent abdominal pain had high amylase levels in their bile at the time of surgery ranging from 800 to 159 000 units/l.

Operative cholangiograms in seven of these patients showed an anomalous junction of their pancreaticobiliary systems and ten also had hyperamylasaemia. Eight of these patients had fusiform dilatation of the extrahepatic ducts whereas it was cystic in the other four (*Table 1*).

Using Todani's modification[12] of the Alonso-Lej classification[13], there were 21 patients with Type I cystic dilatation confined to the common bile duct, 10 with Type I fusiform dilatation of the common bile duct, and one choledochocele (Type III). Two had both intrahepatic and extrahepatic cystic dilatation (Type IV), and there was one with only intrahepatic cystic dilatation (Type V).

Of the various diagnostic procedures, ultrasonography was found to be the most accurate. On the 29 occasions it was used, it was diagnostic in 26 and suggestive in the other three where the duct dilatation was fusiform. Endoscopic retrograde cholangiopancreatography was used on seven occasions in six patients, but its use was restricted to the older children and adults. Percutaneous transhepatic cholangiography was used in six patients but significant bile leakage into the peritoneal cavity was seen on two occasions and the technique is now avoided. Hepatobiliary scintigraphy was used on eight occasions but failed to show the cyst in three patients because of poor concentration of radionuclide.

A correct pre-operative diagnosis was obtained in 28 of the 29 patients investigated as new cases (97 per cent). The single case that was missed was a 6-month-old child diagnosed as biliary atresia after a radionuclide test and liver biopsy.

Seven patients were referred from other hospitals for complications after operations. Five had undergone cystenterostomy, one sphincterotomy and one hepaticoduodenostomy after cyst excision. All presented with recurrent abdominal pain and ascending cholangitis, and two of them had associated variceal haemorrhage from portal hypertension secondary to biliary cirrhosis. The time interval between the first operation and the reconstructive procedure varied from 2 months to 10 years with a mean of 5·5 years.

The operative procedures employed are listed in *Table 2*.

Table 1 *Radiological and laboratory features of patients with raised biliary amylase*

Age	Sex	Serum amylase* (units/l)	Biliary amylase* (units/l)	Type of cyst and radiology
7 years	F	11 000	23 000	I(f), common channel
6 years	F	900	12 000	I(f), common channel
3 years	F	6 900	31 000	I(f), common channel
5 years	M	399	19 000	I(c), unknown
18 months	F	11 300	10 000	I(f), common channel
12 years	F	560	28 000	I(f), common channel
13 years	F	1 156	16 000	I(c), unknown
3 years	F	400	8 000	I(f), common channel
7 years	F	417	159 000	I(f), unknown
13 years	F	178	14 000	I(f), unknown
7 months	F	unknown	800	I(f), common channel
16 years	F	900	18 000	I(c), unknown

* Normal values: serum amylase < 300 units/l, bile amylase < 30 units/l; I(f), Type I fusiform; I(c), Type I cystic

0007-1323/88/090892-04$3.00

Table 2 *Operative procedures performed for choledochal cyst*

Operations	Patients
New cases	29
Primary cyst excision	22
External drainage	4 (3: cyst excised later)
Internal drainage	3 (CCD: 1 CCJ: 2 (1: cyst excised later))
Referred cases	7*
Cyst excision	4
Internal drainage	2 (CCJ)
Roux-en-Y hepatico-jejunostomy (revision)	1 (strictured CCD after cyst excision)

CCD, choledochocystoduodenostomy; CCJ, choledochocysto-jejunostomy; * six were internally drained

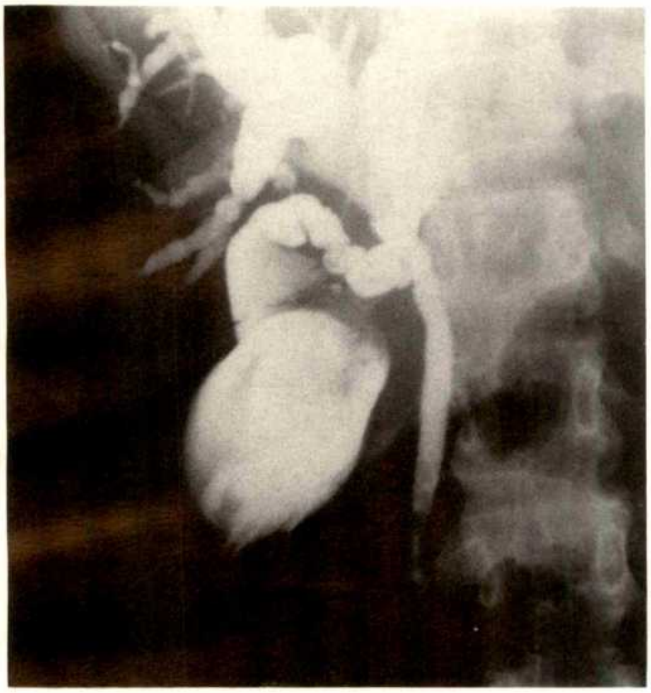


Figure 1 *Type V choledochal cyst in a 12-year-old girl with biliary cirrhosis and portal hypertension*

New cases

Primary excision of the choledochal cysts and Roux-en-Y hepaticojejunostomy were performed in 22 of the 29 patients seen as new cases. Their ages ranged from 3 days to 17 years. The technique we employed has been described previously[3]. The dilated extrahepatic duct is excised with the gallbladder leaving a 'cuff' below the bifurcation of the hepatic ducts for anastomosis to a 45-cm Roux loop of jejunum. On occasions when the portal vein and hepatic artery were adherent due to previous inflammation, the submucosal dissection advocated by Lilly[14] was employed. All these patients have remained well since their surgery.

Three patients who presented earlier in the series had their cysts drained internally with cystenterostomies. Two of them, aged 6 months and 5 years, had choledochocystojejunostomy and the other, aged 5 years, had choledochocystoduodenostomy. The 6-month-old child was well for 10 years before she developed recurrent abdominal pain and jaundice. Her cyst has now been excised and she remains well. The other two patients have been well since their operations.

Four patients had external drainage. The first was a 7-month-old female infant with a spontaneously ruptured cyst. Her postoperative recovery was complicated by septicaemia and her cyst was excised a month later. The second patient suffered cholangitis from an obstructed cyst whilst pregnant (23 weeks gestation). Her common bile duct was drained with a T tube after removal of a large calculus from the lower end. Recovery was satisfactory but the fetus died. The choledochal cyst was excised 3 months later. The third patient was a 39-year-old man who presented with severe cholangitis and hepatorenal failure. Recovery followed biliary decompression with a T tube and his cyst was excised 3 months later without complication. The fourth patient was a 12-year-old girl who presented with severe cholangitis and intermittent oesophageal variceal bleeding. Investigations showed a Type V choledochal cyst, with diffusely dilated and cystic intrahepatic ducts and a normal-size extrahepatic ductal system with an anomalous pancreatobiliary junction (*Figures 1* and *2*). Her liver was cirrhotic and there were signs of portal hypertension. A tube cholecystostomy was performed and debris flushed from the biliary tree. Jaundice subsided after these manoeuvres.

Referred cases

The choledochal cysts were excised in four of the seven patients referred from elsewhere with complications of previous surgery. Choledochocystojejunostomies were refashioned in two patients in whom there were stenoses of previous anastomoses complicated by portal hypertension. The portal hypertension precluded more radical revision surgery. The third patient had developed a strictured hepaticoduodenostomy after a previous cyst excision. This was converted to a Roux-en-Y hepaticojejunostomy.

Results

All 22 patients who had primary cyst excision and the three who had excision after initial external decompression with T tubes remained well from 4 months to 14 years after surgery (mean follow-up 3·5 years) (*Table 3*).

Of the nine patients who had cystenterostomy, five suffered recurrent abdominal pain from pancreatitis or bile stasis with ascending cholangitis and needed subsequent cyst excision. One was well for 10 years after choledochocystojejunostomy before developing recurrent abdominal pain, when investigations showed a dilated biliary tract and stones within the residual cyst. The cyst was excised and she has been well since the operation. One patient with cystenterostomy died from variceal haemorrhage but the remaining three patients are well.

The single patient who had primary cyst excision and a

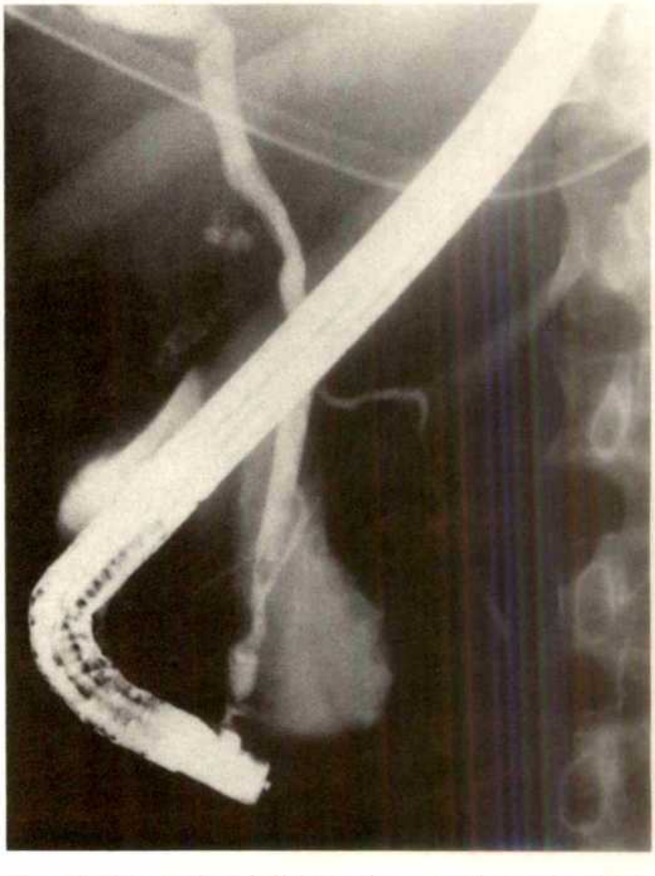


Figure 2 *Common channel of biliary and pancreatic ducts in the girl with Type V cyst (Figure 1)*

Table 3 *Results of surgery*

Operations	Patients	Outcome
New cases		
Primary cyst excision	22	All alive and well
Internal drainage	3	2 alive and well 1 recurrent cholangitis
External drainage	4	3 alive and well 1 cirrhosis and portal hypertension
Referred cases		
Cyst excision	4	All alive and well
Internal drainage	2	1 died 1 cirrhosis and portal hypertension
Roux-en-Y hepaticojejunostomy (revision of hepaticoduodenostomy)	1	Alive and well

hepaticoduodenostomy elsewhere 8 years previously suffered recurrent cholangitis from a strictured anastomosis. He has been well since reconstruction with a Roux-en-Y hepaticojejunostomy. The remaining patient with diffuse Type V choledochal cyst and biliary cirrhosis will probably need a liver transplant at a later date.

Discussion

Choledochal cyst is a rare but important surgical condition. Untreated cysts are associated with severe complications and are uniformly fatal[4,15]. In this series we encountered twelve cases of pancreatitis, four patients with bouts of severe cholangitis, three patients with variceal bleeding from portal hypertension secondary to biliary cirrhosis and one patient with biliary peritonitis from a ruptured cyst.

The occurrence of the classic triad of jaundice, pain and an abdominal mass varies from 13 to 63 per cent in reported series. In this series it occurred in only 7 of 29 new patients (24 per cent). It tends to be less frequent in infancy and early childhood than in adults[16,17].

Cyst rupture has been described previously[1,18-21], and it usually occurs as a spontaneous event[22,23]. Ohkawa *et al.*[21] reported the association of an anomalous junction between the biliary and pancreatic ductal systems. They attributed the rupture to a weakening of the cyst wall by cholangitis secondary to chronic reflux of pancreatic juice into the biliary system along the common channel which is devoid of a sphincteric mechanism. It has been demonstrated that the maximum pressure in the pancreatic duct is much higher than in the common bile duct[24,25].

Although pancreatitis with recurrent abdominal pain has long been known to complicate choledochal cyst[11,26-28], it was Altman *et al.*[29] who first made reference to its causal relationship[30-32]. It is believed that the associated hyperamylasaemia is due at least in part to the amylase in the bile entering the blood through the denuded epithelium of the cyst wall[33]. Certainly the presence of a raised serum amylase should not delay surgery; we have excised a cyst without complication at a time when the serum amylase measured 11 000 units/l. The serum amylase levels fell rapidly after cyst excision. All seven patients with raised levels of biliary amylase who had cholangiograms showed an anomalous pancreaticobiliary junction, including the patient with a ruptured cyst.

Three of our patients developed biliary cirrhosis and portal hypertension. The first patient with Type IV cystic dilatation died from a massive variceal haemorrhage 6 months after surgery. The second patient underwent repeated injection sclerotherapy. The third patient has diffuse Type V cystic dilatation within the liver.

With improved imaging methods in recent years the incidence of correct diagnosis before surgery has been more than 80 per cent[34-36]. In this series a correct pre-operative diagnosis was achieved in 28 of the 29 new patients (97 per cent). In common with other reports[37-39], ultrasonography was found to be the most useful and accurate diagnostic tool. It is non-invasive, and with the high-resolution real-time scanner the anatomy of the intrahepatic ducts can also be determined accurately. It was diagnostic in 26 of the 29 new patients and suggestive in three where the dilatation was fusiform.

Endoscopic retrograde cholangiopancreatography can be useful[40] but we have limited its use to the older children and adults. Operative cholangiography gives good visualization of the intrahepatic ducts and the anatomy of the biliary–pancreatic junction.

Contrary to some reports[41,42], we have found hepatobiliary scintiscanning misleading at times. It failed in three of our eight patients because of poor concentration of radionuclide. However, it is useful for demonstrating the patency of the bile duct–bowel anastomosis after surgery. Computed tomography is not used routinely for patients with suspected choledochal cyst although it might be useful if an associated carcinoma is suspected[43-45].

Complete excision of the cyst and reconstruction by Roux-en-Y hepaticojejunostomy is the treatment of choice and excellent results have been previously reported[11,46,47]. Mortality is low[5,48] and there were no deaths in the present series from surgery. Cyst excision eliminates a reservoir for bile stasis and stone formation. Reflux of pancreatic secretion into the biliary system with resultant cholangitis or pancreatitis is abolished. It removes the site for malignant change which has been estimated to be 20 times higher than for the general population[49]. The technique we employed is well described[3] and the modification suggested by Lilly[14], in which the dissection is performed in the submucosal plane, has been useful in avoiding injury to a very adherent portal vein and hepatic artery.

Choledochocystojejunostomy and choledochocysto-duodenostomy are still popular forms of cyst drainage. However, it is now apparent that the complication and re-operation rate is unacceptably high[10,47,49]. Of three patients who underwent cystenterostomy in the present series two are well but the third developed recurrent abdominal pain, 10 years after surgery, from bile stasis and calculi in the cyst. The cyst was excised and she is now well. Secondary cyst excision was also satisfactory in four of the six patients referred for complications of cystenterostomy performed elsewhere.

Preliminary external drainage with T tubes was very useful in four patients. However, the technique is only necessary as a preliminary procedure in the patients who have either bile peritonitis from a ruptured cyst or cholangitis with or without hepatorenal failure. It is used as a temporary measure and the cyst must be excised at a later date. External drainage has not complicated the subsequent definitive resection.

References

1. Chen WJ, Chang CH, Huang WT. Congenital choledochal cyst: with observation on rupture of the cyst and intrahepatic duct dilatation. *J Pediatr Surg* 1973; **8**: 629–38.
2. Lee SS, Min PC, Kim GS, Hong PW. Choledochal cyst: a report of 9 cases and review of the literature. *Arch Surg* 1969; **99**: 19–28.
3. Howard ER. Choledochal cysts. In: Schwartz SI, Ellis H, ed. *Maingot's Abdominal Operations*. 8th edn. Norwalk, Connecticut: Appleton-Century-Crofts, 1985.
4. Tsardakas E, Robnett AH. Congenital cystic dilatation of the common bile duct: report of 3 cases, analysis of 57 cases and review of the literature. *Arch Surg* 1956; **72**: 311–27.
5. Kimura K, Tsugawa C, Ogawa K *et al.* Choledochal cyst: etiological consideration and surgical management in 22 cases. *Arch Surg* 1978; **113**: 159–63.
6. Arthur GW, Stewart JOR. Biliary cysts. *Br J Surg* 1962; **50**: 671–5.

7 George PA, Maingot R. Choledochal cyst associated with carcinoma in the liver: report of a case. *Br J Surg* 1962; **50**: 339–41.

8. Walton J. Congenital diverticulum of the common bile duct. *Br J Surg* 1939; **27**: 295–315.

9. Pain JA, Cahill CJ, Bailey ME. Management of choledochal cysts in adults. *Proc R Soc Med* 1986; **79**: 22–4.

10 Trout HH, Longmire WP. Longterm follow-up study of patients with congenital cystic dilatation of the common bile duct. *Am J Surg* 1971, **121**: 68–86

11. Miyano T, Suruga K, Chen SC. A clinicopathologic study of choledochal cyst. *World J Surg* 1980; **4**: 231–8

12. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K Classification, operative procedures and review of thirty seven cases including cancer arising from choledochal cyst. *Am J Surg* 1977, **134**: 263–9

13. Alonso-Lej F, Rever WB, Pessagno DJ. Congenital choledochal cyst, with a report of 2 and an analysis of 94 cases. *Int Abstr Surg* 1959; **108**: 1–30.

14. Lilly JR. Total excision of choledochal cyst. *Surg Gynecol Obstet* 1978; **146**: 254–6.

15. Attar S, Obeid S. Congenital cyst of the common bile duct: a review of the literature and a report of 2 cases. *Ann Surg* 1955; **142**: 289–95.

16. Fonkalsrud EW, Boles ET Jr Choledochal cysts in infancy and childhood. *Surg Gynecol Obstet* 1965; **121**: 733–42.

17. Lindenauer S, Lavanway JM. Surgical management of choledochal cyst. *Surgery* 1969; **65**: 972–7.

18. Chesterman JT Choledochal cyst complicating pregnancy and puerperium *J Obstet Gynecol Br Emp* 1944; **51**: 512–18.

19. Friend WD. Rupture of choledochal cyst during confinement. *Br J Surg* 1958; **46**: 155–7.

20 Jackson BT, Saunder P. Perforated choledochal cyst. *Br J Surg* 1971; **58**: 38–42.

21. Ohkawa H, Takahashi H, Maie M. A malformation of the pancreaticobiliary system as a cause of perforation of the biliary tract in childhood. *J Pediatr Surg* 1977; **12**: 541–6

22. Tagart REB. Perforation of a congenital cyst of the common bile duct. *Br J Surg* 1956; **44**: 18–21.

23. Yamashiro Y, Sato M, Hoshino A. Spontaneous perforation of a choledochal cyst. *Eur J Pediatr* 1982, **138**. 193–5.

24. Hess W. *Surgery of the Biliary Passages and the Pancreas.* Princeton: Van Nostrand, 1965.

25. Tanaka M, Ikeda S, Kawakami K, Nakayama F. The presence of a positive pressure gradient from pancreatic duct to choledochal cyst demonstrated by duodenoscopic microtransducer manometry: due to pancreaticobiliary reflux. *Endoscopy* 1982; **14**: 45–7.

26. Blumenstock DA, Mithoefer J, Santulli TV. Acute pancreatitis in children. *Pediatrics* 1957, **19**: 1002–10

27. Buntain WL, Wood JL, Wooley MM. Pancreatitis in childhood. *J Pediatr Surg* 1978; **13**: 143–9.

28. Cuschieri A, Davies RS. Acute pancreatitis complicating a choledochal cyst. *Br Med J* 1969, **iii**: 109

29 Altman MS, Halls JM, Douglas AP, Renner IG. Choledochal cyst presenting as acute pancreatitis. evaluation with ERCP. *Am J Gastroenterol* 1978; **70**: 514–19.

30 Matsusue S, Kashihara S, Nakamura Y, Masumoto H. Role of unusually long common pancreatico-biliary channel as a cause of relapsing pancreatitis in children. *Z Kinderchir* 1982; **36**: 69–72

31. Okada A, Oguchi Y, Kamata S, Ikeda Y, Kawashima Y, Saito R. Common channel syndrome: diagnosis with endoscopic retrograde cholangio-pancreatography and surgical management. *Surgery* 1983; **93**: 634–42.

32. Todani T, Watanabe Y, Fujii T, Toki A, Uemura S, Koike Y. Cylindrical dilatation of the choledochus. a special type of congenital bile duct dilatation *Surgery* 1985; **98** 964–8.

33 Stringel G, Filler RM. Fictitious pancreatitis in choledochal cyst. *J Pediatr Surg* 1982, **17**: 359–61.

34. Kasai M, Asakula Y, Taira Y. The surgical treatment of choledochal cyst. *Ann Surg* 1970; **172**: 844–51

35. Kobayashi A, Ohbe Y. Choledochal cyst in infancy and childhood, analysis of 16 cases *Arch Dis Child* 1977, **52**: 121–8.

36. Saito S, Ishida M. Congenital choledochal cyst *Progr Pediatr Surg* 1974; **6**: 63–90.

37. Kangarloo H, Sartii AA, Sample WF, Amundson G Ultrasonographic spectrum of choledochal cysts in children *Pediatr Radiol* 1980; **9**: 15–18.

38. Markle BM, Potter BM, Majd M. The jaundiced infant and child. *Semin Ultrasound* 1980; **1**: 123–33.

39. Suruga K, Hirai Y, Nagashima K, Wagai T, Inui M. Ultrasonic echo examination as an aid in the diagnosis of congenital bile duct syndrome. *J Pediatr Surg* 1969, **4**: 452–6.

40 Marshall JB, Halpin TC Choledochocele as the cause of recurrent obstructive jaundice in childhood: diagnosis with ERCP. *Gastrointest Endosc* 1982, **28**: 88–90.

41. Huang MJ, Liaw YF. Intravenous cholescintigraphy using Tc 99m-labelled agent in the diagnosis of choledochal cyst *J Nucl Med* 1982, **23**: 113–16.

42. Paramsothy M, Somasundaram K. Technetium 99m-diethyl-IDA hepatobiliary scintigraphy in the preoperative diagnosis of choledochal cyst. *Br J Radiol* 1981, **54**: 1104–7

43. Araki T, Itai Y, Tasaka A CT of choledochal cyst *Am J Radiol* 1980; **135**: 729–34.

44. Cholankeril JV, Ketyer S, Joshi R. Demonstration of choledochal cyst by computed tomography. *Comput Radio* 1982; **6**: 109–14

45. Nakata H, Nobe T, Takahashi M, Maeda T, Koga M. Choledochal cyst. *J Comput Assist Tomogr* 1981; **5**: 99–101.

46 Jones PG, Smith ED, Clarke AM, Kent M. Choledochal cysts: experience with radical excision. *J Pediatr Surg* 1971, **6** 112–20.

47. Somasumdaram K, Wong TJ, Tan KC. Choledochal cyst: a review of 25 cases. *Aust NZ J Surg* 1985, **55**: 443–6.

48. Flanigan DP. Biliary cysts. *Ann Surg* 1975, **182**. 635–42

49 Lilly JR. The surgical treatment of choledochal cyst *Surg Gynecol Obstet* 1979; **149**: 36–42.

Paper accepted 22 May 1988

Br. J. Surg. 1988, Vol. 75, September, 896–898

Endoscopic removal of retained stones after biliary surgery

M. E. Lambert, D. F. Martin and D. E. F. Tweedle

Departments of Surgery and Radiology, University Hospital of South Manchester, Manchester, UK

Correspondence to:
Dr D. F. Martin, Radiology Department, Gastroenterology Unit, University Hospital of South Manchester, Manchester
M20 8LR, UK

Seventy-three patients with retained stones in the common duct after biliary surgery underwent attempted endoscopic removal at a mean interval of 39 days after surgery. Endoscopic extraction was successful in 63 patients (86 per cent). Complications occurred in 14 patients (19 per cent). The most frequent complication was haemorrhage which occurred in nine patients, four of whom required surgery; two other patients required surgery for complications. The complication rate of endoscopic sphincterotomy in recently operated patients may be higher than in the non-operated patient. Less invasive methods, such as dissolution therapy or T tube track extraction, may be preferable as they are associated with less risk. Endoscopic sphincterotomy should be reserved for patients in whom these alternative techniques fail or are inappropriate.

Keywords: Retained stones, endoscopic sphincterotomy

The unhappy discovery of retained gallstones on a T tube cholangiogram after exploration of the common bile duct is not uncommon and may occur in up to 15 per cent of such operations[1–7]. If stones are small they may pass spontaneously[8], but in many they will have to be removed[9,10]. Further surgical exploration has higher mortality and morbidity[6,11–14] and is less successful than first exploration, stones being retained after as many as one-third of repeat attempts and after a still higher proportion of third or subsequent operations[4,15,16].

There are alternatives to surgery for retained stones. If saline or heparinized saline is flushed down the T tube, stones may be washed into the duodenum, especially if they are small[17], distal to the T tube[8] and the sphincter of Oddi is relaxed with glyceryl trinitrate[18], glucagon[19] or ceruletide[20,21], a method which may be effective in up to 50 per cent of selected patients. In addition simply to flushing stones from the ducts, attempts have been made to dissolve stones with ether or chloroform. This may prove too toxic[22] but the use of cholate[13], mono-octanoin[23,24] or methyl tertiary butyl ether[25] has met with varied success. The value and limitations of these agents have been reviewed by Neoptolemos *et al.*[26] who also point out that volatile dissolution agents can dissolve the T tube as well as the stones.

Stones may be removed via the T tube track using the Burhenne steerable extraction catheter[27,28] but this requires a delay in treatment while a wide, mature track forms, although success with earlier extraction has been reported[29]. Reports of success vary[28,30]. Endoscopic sphincterotomy with stone extraction is a safe and effective means of removing stones from the common bile duct without surgery[31,32]. We report our experiences with 73 patients treated by endoscopic sphincterotomy for stones retained in the common bile duct after surgery.

Patients and methods

Seventy-three patients were referred with retained stones in the common bile duct 2–18 weeks after biliary surgery between January 1980 and December 1985. There were 51 women (mean age 69 years) and 22 men (mean age 65 years). Of these, 69 patients had undergone exploration of the common bile duct, in 3 exploration had not been attempted despite the presence of stones and in 1 an emergency cholecystostomy had been performed. Fifty-nine patients had a T tube *in situ* and in ten the T tube had been removed, resulting in biliary fistula in two. The mean time since operation was 39 days (range 14–126). In four patients mono-octanoin infusion via the T tube had been performed without successful dissolution and this had delayed referral to a mean of 104 days (range 82–126). In patients with T tubes who had not undergone attempts at chemical dissolution, the mean time between operation and endoscopic sphincterotomy was 30 days.

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy were performed by one of two clinicians (D.F.M. and D.E.F.T.) using standard methods already described in detail[33]. All patients were given mezlocillin 2 g IV before the procedure.

Results

Seventy-three patients underwent endoscopy but in two the papilla, distorted by previous surgery, could not be cannulated and ERCP was not possible. Both these patients underwent surgery, as did two others in whom the retained stones shown on ERCP were considered too large for endoscopic removal and in whom endoscopic sphincterotomy was not undertaken. One patient in whom bleeding from endoscopic sphincterotomy precluded attempts at stone extraction at the first attempt declined a second endoscopy and later underwent reoperation. In five patients, complications—bleeding, cholangitis and an impacted extraction basket—precipitated emergency operation before the stones could be cleared. We failed to extract the stones endoscopically in 10 patients.

In all 63 patients successfully treated, eventual clearance of the ducts was demonstrated by ERCP. Our policy is to repeat ERCP until the ducts are proved to be clear; 32 patients required a second attempt and of these, 9 required a third, 6 a fourth and 1 a fifth attempt before clear ducts were demonstrated. A mean of 1·6 endoscopies per patient was required.

Complications

The most common complication was bleeding which, defined by the strict criterion of a fall in Hb of 2 g/dl or more, occurred after endoscopic sphincterotomy in nine patients (12 per cent). Of these, six required transfusion (8 per cent) and four of these (5 per cent) required emergency operation at which the retained stones were removed and haemostasis was secured. All survived.

Of the six patients requiring transfusion, all had bled heavily immediately after endoscopic sphincterotomy; their Hb had fallen by more than 4 g/dl and their mean transfusion requirement was 5 units. Of the four patients who underwent surgery, all had clinical evidence of continued bleeding despite transfusion. The decision to operate was not influenced by failure to clear ducts of stones after endoscopic sphincterotomy.

Acute pancreatitis with abdominal pain and a serum amylase level of more than 1000 units/l occurred in two patients and prolonged their in-patient stay from the usual 24 h to 4 and 8 days. Both recovered and remained well.

Acute cholangitis occurred in two patients. In one this followed endoscopic sphincterotomy with unsuccessful attempts at extraction and was treated with vigorous antibiotic therapy; the retained stone was removed at subsequent ERCP. In the second, cholangitis complicated nasobiliary perfusion with cholate after a fourth attempt at extraction had failed. Its onset provoked surgical removal of the stone and drainage of the common bile duct.

A morbidly obese 43-year-old man with cholangitis and jaundice suffered impaction of the extraction basket and gallstone after sphincterotomy. His common bile duct stone had been purposely left without exploration of the duct at previous cholecystectomy. Surgery was required to remove the basket and stone but he died of metabolic and respiratory complications.

There were 14 complications in all, i.e. in 19 per cent of patients or 12 per cent of endoscopic procedures.

Deaths

Two patients died within 30 days of ERCP. One death followed the complication of an impacted extraction basket described above. Another, elderly patient had undergone six surgical explorations of her common bile duct; endoscopic extraction was unsuccessful. She underwent her seventh surgical exploration of the common bile duct and died of complications.

Discussion

This study evaluates our experience in removing retained stones; we have included all patients referred for consideration of endoscopic removal and all complications occurring within 30 days of endoscopy.

A successful sphincterotomy was achieved in 69 of 73 patients (95 per cent) (although in two it was deliberately not attempted because the stone was considered too large for endoscopic extraction). This proportion is broadly similar to other reported series[32] though rather better than our own results in all patients presenting with stones in the common bile duct, in which a sphincterotomy was achieved in 88 per cent[34]. The ducts were cleared in 63 of 73 patients (86 per cent), a proportion similar to our own results for all cases (79 per cent)[34].

It is not clear from other reports how many attempts were required before clearance of the ducts was achieved; in our series a mean of 1·6 endoscopies per patient was required. O'Doherty *et al.*[8] imply that, of 39 patients, only 2 required a second endoscopy to complete endoscopic sphincterotomy or stone extraction, in which case their success rate at first attempt is much better than ours. In our series, 32 patients (44 per cent) underwent a second ERCP although in 11 of these the cholangiogram showed that the ducts had cleared as a result of the first procedure.

The striking feature of this experience is the incidence of complications, which occurred in 14 patients (19 per cent) and which led to emergency operation in 6. Our own previously reported complication rate[34] for endoscopic stone removal in all cases (12·3 per cent of patients) was also rather higher than most, possibly because of the very strict criterion adopted for the definition of bleeding. Even so, six patients required transfusion and four required urgent surgery.

We (J. C. McGregor, D. F. Martin, M. E. Lambert and D. E. F. Tweedle, unpublished results) and others[35] have evaluated risk factors for complications after endoscopic sphincterotomy. In our series of 383 patients, the independent significant factors associated with complications were found to be low serum albumin, raised serum creatinine, raised blood white cell count and a history of previous biliary surgery. All patients studied in this report had, of course, undergone surgery but the incidence of the other risk factors was no higher than for all patients with stones in the common bile duct. It may be that distortion or perhaps oedema of the papilla resulting from surgery may be responsible for the high complication rate, particularly from bleeding. In the Leicester series[35] elevated serum bilirubin concentration was also a risk factor for postendoscopic sphincterotomy complications, although this is not our experience (J. C. McGregor, D. F. Martin, M. E. Lambert and D. E. F. Tweedle, unpublished work). In patients with freely draining T tubes the serum bilirubin is likely to be near normal and they should be at low risk. Endoscopic removal has a greater success rate and a similar complication rate[31] when compared with surgery, especially in elderly patients. To reduce the complications associated with treatment of retained stones it may be wisest to attempt flushing or dissolution of stones first, possibly followed by extraction via the T tube track if necessary. Although the success and complication rates of this procedure are variable[28,30], in experienced hands the success rate is high (95 per cent) and the morbidity low (4 per cent); Burhenne reports no deaths in 661 patients[28]. These results are better than any reported for endoscopic sphincterotomy. In addition to steerable catheter extraction, percutaneous common duct stone extraction using the flexible choledochoscope also appears to be a safe, effective method of dealing with retained stones[36,37]. Although endoscopic sphincterotomy has the considerable advantage that treatment can be carried out as soon as retained stones are discovered, in some patients treatment may be unnecessary as stones may pass spontaneously[8]. Endoscopic sphincterotomy may be best employed when less invasive procedures are inappropriate or have failed.

References

1. Glenn F. Retained calculi within the biliary ductal system. *Ann Surg* 1974; **179**· 528–39.
2. Way LW, Admirand WH, Dunphy JE. Management of choledocholithiasis. *Ann Surg* 1972; **176**: 347–59.
3. Greenall MJ, Gough MH, Kettlewell MG, Nolan DJ. Non-operative removal of retained biliary tract stones. *J R Coll Surg Edinb* 1982; **27**: 63–5
4. Girard RM, Legros G. Retained and recurrent bile duct stones; surgical and non-surgical removal. *Ann Surg* 1981; **193** 150–4
5. Crumplin MKH, Jenkinson LR, Kassob JY, Whitaker CM, Al-Boutiahi FH. Management of gallstones in a district general hospital. *Br J Surg* 1985; **72**· 428–32.
6. Vellacott KD, Powell PH. Exploration of the common bile duct. a comparative study. *Br J Surg* 1979; **66**: 389–91.
7. Kappes SK, Adams MB, Wilson SD. Intraoperative biliary endoscopy: mandatory for all common duct operations? *Arch Surg* 1982; **117**: 604–7.
8. O'Doherty DP, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for retained common bile duct stones in patients with T-tube in situ in the early postoperative period. *Br J Surg* 1986; **73**: 454–6.
9. Hicken NF, McAllister AJ. Operative cholangiography as an aid in reducing the incidence of overlooked bile duct stones. *Surgery* 1964; **55**, 753–8.
10. Bergdahl L, Holmund DEW. Retained bile duct stones *Acta Chir Scand* 1976; **142**: 145–9.
11. Lygidakis NJ. Surgical approaches to recurrent choledocholithiasis. *Am J Surg* 1983; **145**· 633–9.
12. McSherry CK, Glenn F. The incidence and causes of death following surgery for non-malignant biliary tract disease *Ann Surg* 1980; **191**· 271–5.
13. Mack E, Patzer EM, Crummy AB, Hofmann AF, Babayan VK Retained biliary tract stones *Arch Surg* 1981; **116**· 341–5.
14. Choi TK, Lee NW, Wong J, Ong GB. Extraperitoneal sphincteroplasty for residual stones. *Ann Surg* 1982, **196**: 26–9.
15. Allen B, Shapiro H, Way LW Management of recurrent and residual common duct stones. *Am J Surg* 1981; **142**: 41–7.
16. Kune GA. *Current Proceedings in Biliary Surgery.* Boston. Little Brown, 1972: 221–4.
17. Motson RW. Dissolution of common bile duct stones. *Br J Surg* 1981; **68**: 203–8.
18. Staritz M, Poralla T, Ewe K, Meyer Zum Buschenfelde K-H. Effect of glyceryl trinitrate on the sphincter of Oddi motility and baseline pressure. *Gut* 1985; **26**: 194–7.

19. Paul F. The role of glucagon in the treatment of biliary tract pathology. In Picazo J, ed. *Glucagon in Gastroenterology* Lancaster MTP, 1979: 107–20.
20. Cuschieri A. Management of retained biliary calculi: relaxation of the sphincter induced by ceruletide. *Br Med J* 1984; **289**: 1582.
21. Walker SJ, Mackie CR, Mendelson RM, Arnold A, Colmer MR. Ceruletide for retained biliary stones. *Br Med J* 1986; **293**: 595–6.
22. Glenn F. Common duct exploration for stones. *Surg Gynecol Obstet* 1952; **95**: 431–8
23. Thistle JL, Carlson GL, Hofman AF. Monooctanoin, a dissolution agent for retained cholesterol bile duct stones: physical properties and clinical application. *Gastroenterology* 1980; **78**: 1016–22.
24. Palmer KR, Hofman AF. Intraductal monooctanoin for the direct dissolution of bile duct stones: experience in 343 patients. *Gut* 1986; **27**: 196–202.
25. Allen MJ, Borody TJ, Buglios TF, May GR, LaRusso NF, Thistle JL Rapid dissolution of gallstones by methyl tertbutyl ether. *New Engl J Med* 1985; **312**: 217–20.
26. Neoptolemos JP, Hofmann AF, Moossa AR. Chemical treatment of stones in the biliary tree. *Br J Surg* 1986; **73**: 515–24.
27. Burhenne HJ. Non-operative extraction of retained bile duct stones. *World J Surg* 1978; **3**: 439–45.
28. Burhenne HJ. Percutaneous extraction of retained biliary tract stones. *Am J Radiol* 1980; **134**: 888–98.
29. Hublitz UF, Cogliano FD, Arena PJ. Early extraction of residual biliary tract stones: A two guide-wire technique. *AJR* 1984; **143**: 1090–92.
30. Mason R. Percutaneous extraction of retained gallstones via the T-tube track—British experience of 131 cases. *Clin Radiol* 1980; 1: 497–9.
31. Neoptolemos JP, Carr-Locke DL, Fraser I, Fossard DP. The management of common bile duct calculi by endoscopic sphincterotomy in patients with gallbladders in situ. *Br J Surg* 1984; **71**: 69–71.
32. Cotton PB. Endoscopic management of bile duct stones (apples and oranges). *Gut* 1984; **25**: 587–97.
33 Martin DF, Tweedle DEF Endoscopic management of common duct stones without cholecystectomy. *Br J Surg* 1987; **74**. 209–12.
34. Lambert ME, Martin DF, Tweedle DEF. Endoscopic removal of stones from the common bile duct—the whole truth. *Gut* 1986, **27**: A1280.
35. Neoptolemos JP, Shaw DE, Davidson BR, Carr-Locke DL. Multivariate analysis of risk factors in patients undergoing surgery and/or endoscopic sphincterotomy (ES) for common bile duct (CBD) stones. *Gut* 1987; **28**: A1383.
36. Choi TK, Lee MJR, Lui R, Fok M, Wong J. Postoperative flexible choledochoscopy for residual primary intrahepatic stones. *Ann Surg* 1986; **203**: 260–65.
37. Hwang MH, Lee HH, Lin J, Yang J-C, Yueh S-K. Transcholecystic endoscopic choledocholithotripsy: successful management of retained common bile duct stone. *Endoscopy* 1987, **19**: 24–7.

Paper accepted 30 April 1988

Br. J. Surg. 1988, Vol. 75, September, 899–900

Cholelithiasis: a serious complication after total gastrectomy

P. Hauters, A. de Neve de Roden, A. Pourbaix, F. Aupaix, P. Coumans and G. Therasse

Department of Surgery, Hôpital de Jolimont, Rue Ferrer 159, 7161 Haine-Saint-Paul, Belgium

Correspondence to: Dr P Hauters, 51 rue du Placard, 6508 Carnières, Belgium

To establish the incidence of cholelithiasis after total gastrectomy, patients operated on between 1979 and 1985 were reviewed. The study group consisted of 30 patients, all free of gallstones at the time of their gastrectomy. The median age of the patients was 56 years, the average follow-up 40 months. Cholelithiasis developed in 47 per cent of patients (14/30) and always within 2 years of total gastrectomy. The incidence of cholelithiasis was not related significantly to the sex or age of the patients. Morbidity from cholelithiasis was not negligible. Three of the fourteen patients presenting with gallstones required medical treatment in hospital and later came to cholecystectomy because of specific biliary symptoms. Cholelithiasis appears to be a significant complication after total gastrectomy. It may be related to the vagotomy which is performed at the time of gastrectomy.

Keywords: Cholelithiasis, gastrectomy, vagotomy

It is our practice to perform total gastrectomy in patients with malignant stomach tumours whenever resection is thought to be curative. A complete postoperative check-up, including ultrasonographic abdominal examination, is generally carried out twice a year. Cholelithiasis was often detected, even though these patients had a normal gallbladder before surgery. Although gallstone disease is reported to be a sequel of gastric surgery and vagotomy in particular, the subject has remained controversial. In the present study, the occurrence of cholelithiasis after total gastrectomy was analysed.

Patients and methods

The records of 40 patients who underwent total gastrectomy in the Department of Surgery at Jolimont Hospital, Haine-Saint-Paul between 1979 and 1985 were reviewed. Only 30 of the 40 were included in the study for the following reasons. Ten patients could not be considered as two had previously undergone cholecystectomy, three died within a few months of surgery, and the pre-operative finding of gallbladder disease in five led to cholecystectomy at the time of gastrectomy

Among the study group, gastrectomy was carried out in 29 cases for carcinoma and in 1 case for multiple ulceration Gastrointestinal continuity was restored in 25 cases by a Henle loop, in 4 by a Roux-en-Y loop and in 1 by a Tomoda loop. The median age at the time of operation was 56 years (range 36–77 years). There were 18 men (median age 54 years) and 12 women (median age 61 years) On average, patients have been followed for 40 months (range 12–84 months). The follow-up of the patients developing gallstones was almost the same as that of the patients retaining a normal gallbladder after operation (42 and 38 months, respectively). At the time of gastrectomy, the normality of the gallbladder and lack of stones were verified in all the patients by careful operative palpation. Before gastrectomy, two patients had been subjected to an intravenous cholangiogram and twenty to abdominal ultrasonography, demonstrating in all cases a normal gallbladder All the patients were regularly submitted to ultrasonography following gastrectomy These examinations were performed primarily to detect the presence of hepatic metastases, but included careful examination of the gallbladder. In the present study, cholelithiasis after gastrectomy was defined as gallstones visible on ultrasonography. Finally, we also tried to determine the clinical implications of such gallstone disease and attempted to define patient groups prone to that complication

Results

Ultrasonographic abdominal examination demonstrated that gallstones developed in 14 of the 30 gastrectomized patients (47 per cent). Cholelithiasis frequently developed soon after total gastrectomy (*Table 1*); indeed, 11 patients developed gallstones within 1 year of the operation. After the second year, no new gallstones were diagnosed

Cholelithiasis incidence was also analysed in relation to the sex and the age of the patients: 8 women out of 12 (67 per cent), 6 men out of 18 (33 per cent), 9 patients over the age of 55 out of 16 (56 per cent) and 5 patients aged 55 or under out of 14 (36 per cent) developed gallstones. Statistical analysis (χ^2 test) indicated that within this small sample no patient group appeared particularly prone to developing gallstones.

Cholelithiasis morbidity among the study group was not negligible. Two years after total gastrectomy, one female patient, aged 59, was admitted because of acute cholecystitis and had to undergo emergency operation. Respectively 2 and 3 years after surgery, a woman aged 67 and a man aged 46 presented with biliary colic, fever and icterus. After the acute attack, medical treatment with chenodeoxycholic acid was started but without success so that cholecystectomy had to be performed. Thus 43 per cent (3/7) of the patients surviving 5 years after gastrectomy and presenting with gallstones required cholecystectomy for specific biliary symptoms.

It is to be noted that further investigation with intravenous cholangiogram or cholecystography was performed in eight patients (including the above-mentioned three cholecystectomized patients). Gallstones were radiolucent in all patients, multiple in four of them, and usually <1 cm in diameter. The radiolucent nature of the stones did not give us a precise clue about the chemical nature of the gallstones but two of the three cholecystectomized patients had their gallstones analysed for chemical components. This revealed a pigment stone in the first

Table 1 *Incidence of cholelithiasis after total gastrectomy*

		Cholelithiasis	
Follow-up (years)	Number of patients	Recent diagnosis	Incidence (%)
1	30	11	11/30 (37)
2	23	3	12/23 (52)
3	21	0	10/21 (48)
4	17	0	9/17 (53)
5	14	0	7/14 (50)

0007-1323/88/090899-02$3 00

case and a calcium bilirubinate stone in the second although cholesterol stones had been expected. This enabled us to understand why treatment with chenodeoxycholic acid had been unsuccessful.

Discussion

In the present study we have demonstrated that within 2 years of total gastrectomy, 52 per cent (12/23) of the patients who had a normal gallbladder at the time of operation produced gallstones (*Table 1*). It has been shown that the prevalence of gallstone disease among a 60-year-old standard population is about 10 per cent[1] and it appears likely that cholelithiasis in our patients was a sequel of total gastrectomy. Furthermore, in our study group, 22 patients had good pre-operative objective evidence of an absence of gallstones. In the case of the other eight patients, it could be claimed that peroperative palpation gave falsely negative findings regarding gallstones. However, in our experience, operative palpation has always been in good agreement with pre-operative investigations and it appears to be a reliable means of assessing gallbladder normality. Only four of these eight patients developed gallstones and this was the same proportion as that seen in the whole group. Furthermore, gallstone disease after gastrectomy was defined as visible stones at ultrasonography. If anything, the incidence of cholelithiasis might be underestimated by this definition.

Although the matter remains controversial[2], several clinical studies have pointed out the increased incidence of cholelithiasis after truncal vagotomy. That incidence varies from 9 to 21 per cent with a follow-up generally >5 years[3–7]. Gastrectomy in addition to truncal vagotomy could increase the risk of gallstone disease[4,8]. Preservation of the extragastric branches of the vagus nerves as achieved by selective vagotomy or parietal cell vagotomy ensures normal function of the gallbladder and reduces the incidence of gallstone development[4–8]. After truncal vagotomy, dilatation and unsatisfactory emptying of the gallbladder result in stasis which could encourage subsequent stone formation[5,7,9,10]. 'Increased resistance to flow through the sphincter of Oddi may represent the initial step leading to gallbladder dilatation, bile stasis and ultimately gallstone formation'[11]. In contrast, some authors have shown that neither gallbladder filling nor gallbladder emptying in response to cholecystokinin stimulation was altered by vagotomy[12,13]. Some animal experiments[14,15] have demonstrated a post-vagotomy increase in bile lithogenic index (fall in bile acid concentration and/or rise in cholesterol concentration). Human studies, on the other hand, have failed to establish a trend toward bile lithogenicity after vagotomy[13,16]. In patients with truncal vagotomy, impaired pancreatic enzyme secretion in response to nutrients has been observed. As the pancreas responded normally to exogenous hormonal stimulation, it was suggested that vagotomy could reduce the amount of cholecystokinin released from the intestinal mucosa[17,18]. Yet, Hopman *et al.* who used a radioimmunoassay instead of bioassay to measure plasma cholecystokinin concentration, did not confirm those results[19].

While no clear mechanism can be determined, it appears that gallbladder dysfunction is related to section of the hepatic branches of the vagus nerves[20]. As Griffith[10] rightly points out, anatomical dissections indicate that incomplete hepatic vagotomy quite frequently occurs in the course of truncal vagotomy, particularly in patients whose hepatic vagus nerves arise proximally and lie adjacent to the right crus, well removed from the oesophagus. The variable rate of incomplete hepatic vagotomy probably results in a variable rate of biliary sequelae.

This concept may be applied to the high incidence of cholelithiasis observed after total gastrectomy. The surgical procedure includes a complete section of the lower oesophagus and of the lesser omentum with ligature of the left gastric artery at its base. Therefore, except for aberrant vagus nerves, total gastrectomy implies complete hepatic vagotomy.

Gallstones were produced soon after gastrectomy as 79 per cent (11/14) of the cases were diagnosed within a 1 year follow-up. On the other hand, beyond the second year no new gallstone was discovered. Miller[21] also found that gallstones appeared within 7–32 months of truncal vagotomy. In dogs, Tompkins *et al.*[3] have recorded the presence of lithogenic bile after vagotomy. However, the lithogenicity disappeared within an 8-week postoperative period. Consequently, as Rehnberg and Haglund[8] have reported, predisposition to gallstones may be transitory.

Morbidity of cholelithiasis was not negligible in our patients. We have also shown that chenodeoxycholic acid is not always a reliable treatment. If our data can be confirmed by other authors, one may in future advise routine cholecystectomy when carrying out total gastrectomy.

References

1. Kern F. Epidemiology and natural history of gallstones. *Semin Liver Dis* 1983; **3**. 87–96.
2. Mujahed Z, Evans JA. The relationship of cholelithiasis to vagotomy. *Surg Gynecol Obstet* 1971; **133**: 656–8.
3. Tompkins RK, Kraft AR, Zimmerman E, Lichtenstein JE, Zollinger RM. Clinical and biochemical evidence of increased gallstone formation after complete vagotomy. *Surgery* 1972; **71**. 196–9.
4. Ihasz M, Wachtl I, Kiss L, Koiss I. Incidence of cholelithiasis after truncal and selective vagotomy. *Acta Chir Acad Sci Hung* 1977; **18**: 115–21.
5. Sapala MA, Sapala JA, Resto Soto AD, Bowman DL. Cholelithiasis following subtotal gastric resection with truncal vagotomy *Surg Gynecol Obstet* 1979; **148**: 36–8.
6. Clave RA, Gaspar MR. Incidence of gallbladder disease after vagotomy. *Am J Surg* 1969; **118**: 169–76.
7. Ihasz M, Griffith CA. Gallstones after vagotomy. *Am J Surg* 1981; **141**: 48–50.
8. Rehnberg O, Haglund U. Gallstone disease following antrectomy and gastroduodenostomy with or without vagotomy. *Ann Surg* 1985; **201**: 315–8.
9. Johnson FE, Boyden EA. The effect of double vagotomy on the motor activity of the human gallbladder. *Surgery* 1952; **32**: 591–601.
10. Griffith CA. Relationship between vagotomy and/or gastrectomy and the development of cholelithiasis (letter). *Ann Surg* 1983; **197**: 120–1.
11. Pitt HA, Doty JE, Roslyn JJ, Den Besten L. The role of altered extrahepatic biliary function in the pathogenesis of gallstones after vagotomy. *Surgery* 1981; **90**: 418–25
12. Pellegrini CA, Lewin M, Patti MG, Thomas MJ, Ryan T, Way LW. Gallbladder filling and response to cholecystokinin are not affected by vagotomy. *Surgery* 1985; **98**: 452–8.
13. Schaffer EA. The effect of vagotomy on gallbladder function and bile composition in man. *Ann Surg* 1982; **195**: 413–8.
14. Cowie AGA, Clark CG. The lithogenic effect of vagotomy. *Br J Surg* 1972; **59**: 365–7.
15. McMaster P, Medd RK, Mcleish RN The influence of vagotomy on bile kinetics in the Rhesus monkey. *Eur Surg Res* 1979, **11**· 191–204.
16. Stempel JM, Duane WC. Biliary lipids and bile acid pool size after vagotomy in man. *Gastroenterology* 1978; **75**: 608–11.
17. Gamble WS, Hofman AF. Impaired pancreozymin secretion after vagotomy and pyloroplasty. *J Lab Clin Med* 1970; **76**: 871–6.
18. Konturek SJ, Becker HD, Thompson JC. Effect of vagotomy on hormones stimulating pancreas secretion. *Arch Surg* 1974; **108**: 704–8.
19. Hopman W, Jansen J, Lamers C. Plasma cholecystokinin response to a liquid fat meal in vagotomised patients. *Ann Surg* 1984; **200**: 693–7.
20. Csendes A, Larach J, Godoy M. Incidence of gallstones development after selective hepatic vagotomy *Acta Chir Scand* 1978; **144**: 289–91.
21. Miller MC. Cholelithiasis developing after vagotomy. *Can Med Assoc J* 1968; **98**: 350–4.

Paper accepted 7 May 1988

For debate

Br. J. Surg. 1988, Vol. 75, September, 901–903

Definitive radiation therapy for selected cancers of the rectum

B. Sischy, E. J. Hinson and D. R. Wilkinson

The Daisy Marquis Jones Radiation Oncology Center, Highland Hospital, 1000 South Avenue, Rochester, New York 14620, USA

Correspondence to: Dr B. Sischy

During the last 15 years, over 400 patients with adenocarcinoma of the rectum have undergone a course of endocavitary irradiation for cure or palliation of Dukes' A and B disease. This treatment method makes use of an unconventional fractionation scheme, by which the tumour receives 10 000–12 000 cGy in approximately four fractions over a period of about 60 days. The treatments are separated by an interval of 2 or 3 weeks. This method of definitive irradiation allows suitable patients to avoid abdominoperineal resection and its drawbacks. Hospitalization is avoided and the patients maintain a normal daily life. Approximately 15–20 per cent of all rectal cancer patients may be expected to fulfil the criteria for selection, which are sufficiently strict that the local control (95 per cent) and 5-year survival rates (94 per cent) can exceed those of surgery for comparable disease.

Keywords: Endocavitary irradiation, rectum, neoplasm, radiation therapy, contact therapy

Sphincter-saving procedures have recently evoked great interest in the treatment of rectal cancer. A number of protocols is evolving in an attempt to identify optimal methods of local treatment. Following the pioneering work of Papillon[1] it has become apparent that endocavitary irradiation has a variety of advantages over other treatment methods for appropriate patients. An abdominoperineal resection with its associated colostomy and incidence of male impotence is avoided. The treatment is without any risk of mortality and has only minimal local morbidity. Patients are treated on an outpatient basis, they do not require general anaesthesia and can continue normal daily activities without loss of work time. Due to the nature and the quality of the X-ray beam used in this technique, perforation of the rectal wall does not occur and a high dose may be delivered to the tumour bed with minimal irradiation of the surrounding tissues. Patients may be followed without special facilities as sigmoidoscopy gives clear visualization of the rectal wall. Should a patient develop a second lesion in the rectum or a recurrence of the original lesion, radical surgery is not precluded. As the volume of tissue treated is minimal, surgical techniques and postoperative healing are not compromised.

This review examines our own results using this approach in patients with rectal cancer.

Patients and methods

Selection of patients

When offering patients local treatment as an alternative to radical excision, it is important to achieve results equal to those of traditional therapy. For this reason strict criteria must be applied to ensure patient suitability. At present it is estimated that approximately 15–20 per cent of patients with carcinoma of the rectum may be suitable for this method of treatment[2].

The lesion should be Dukes' A. According to Morson's review of surgical specimens[3], lesions of this stage exhibit a probability of perirectal lymph node involvement of less than 10 per cent. The rectal mucosa must be examined by very careful digital palpation to exclude the presence of perirectal nodes.

Although digital examination by an experienced clinician may have an accuracy of over 80 per cent[4] it is now possible to obtain more objective information regarding the extent of the lesion and the status of the perirectal lymph nodes pre-operatively by computed tomographic scanning, nuclear magnetic resonance imaging and transrectal ultrasound[5–8]. Transrectal ultrasound appears able to provide optimal information in our own unpublished comparison of the three methods.

The lesion should be mobile as fixation indicates penetration through the muscularis into the serosa or perirectal fat. The diameter of the lesion should be no greater than 5·0 cm. The treatment proctoscope allows a 2·9 cm target volume to be treated and lesions up to 5 cm may be treated by overlapping fields. The tumour must lie distal to the peritoneal reflection and must not encroach across the dentate line into the anal canal. The modified squamous epithelium of the anal canal is extremely senstive to high doses of irradiation and excessive morbidity would occur if this area were allowed to receive treatment by this technique and fractionation scheme.

Polypoid, exophytic and ulcerative lesions are all suitable for endocavitary irradiation provided the above criteria are fulfilled. It is important to review the histological differentiation of these tumours, and only well or moderately differentiated lesions should be accepted for this treatment. Poorly differentiated lesions are more likely to metastasize, both to perirectal nodes[3] and to distant sites. It may be argued however that these higher grade lesions have such a poor prognosis, even when radical surgery is performed, that in special situations palliative endocavitary irradiation may be an excellent method of gaining local control.

Certain patients may be referred because they are medically inoperable or have refused an abdominoperineal resection. Some of these patients, who do not fit within the selection criteria for this treatment method, can be offered a course of therapy and are then placed into a separate palliative group. Many patients are deemed unsuitable and are not offered endocavitary irradiation because of advanced disease and some are rejected if technical difficulties prevent the adequate delivery of treatment.

Method

Endocavitary irradiation is delivered on an outpatient basis. Patients have an enema before examination and treatment; dietary restrictions are unnecessary. Some patients require local anaesthesia which is administered by perianal block using 1 per cent lignocaine. The patient is positioned on a proctological tilt table. After digital and proctoscopic examinations, using specially designed applicators equipped with fibreoptics, treatment is delivered from a Philips (Philips, Eindhoven, The Netherlands) RT-50 contact machine. The patient is able to resume normal activity immediately after therapy.

From a paper delivered at the 50th Anniversary Conference of Megavoltage Radiotherapy at St. Bartholomew's Hospital, London, September 1987

0007–1323/88/090901–03$3.00

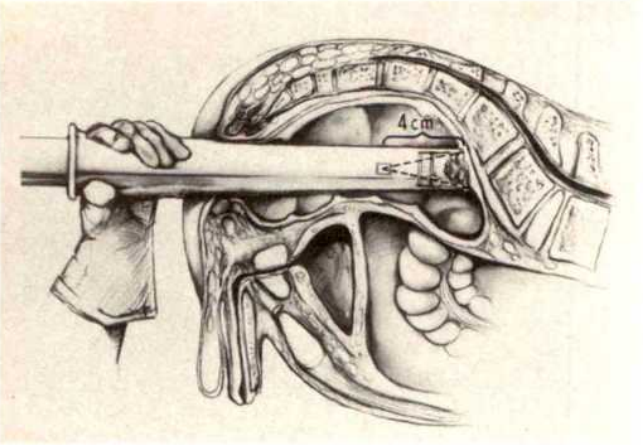


Figure 1 *Diagram to show endocavitary irradiation being delivered*

It is vital that the radiation field remains constant during treatment and, in order to ensure that the lesion is within the target area, the treatment proctoscope must be hand-held in a firm manner. The X-ray tube must likewise be held without any movement (*Figure 1*). The output of the RT-50 is rapid and the treatment time is under 4 min. The radiological protection required is minimal and gowns lined with 1·0 mm of lead for all personnel, and gloves containing 0·5 mm of lead for the operator, are sufficient.

Patients receive a total dose of between 10000 and 12000 cGy in three to four treatments given at intervals of 2–3 weeks over approximately 60 days. If the lesion is larger than 3 cm in diameter, two fields may be treated at each session until sufficient regression has taken place to allow the tumour to be encompassed in one field. This often occurs after the first or second treatment. If a lesion is very small, a treatment proctoscope may be used which allows a field 2·5 cm in diameter to be treated. The majority of patients receive therapy through a 2·9 cm diameter applicator. The 50 per cent isodose line is at 6 mm and it is becoming apparent that the dose distribution is such that it is likely that a number of Dukes' B lesions can be treated. Accurate calibration of the equipment, which has a high output and a short focal source distance, is obviously of great importance.

Patients are followed at regular intervals by digital palpation, direct visualization and laboratory and imaging studies. Biopsies are not routinely performed except when recurrence is suspected.

Special situations

It has been shown by various trials that external beam irradiation can reduce the number of positive perirectal lymph nodes in patients with locally advanced carcinoma of the rectum[9]. It is also known that following external beam irradiation there is a marked decrease in the number of patients presenting with local recurrence[9–13]. There is a group of patients who are referred for treatment with tumours which marginally fit the selection criteria. As in the palliative group, some have refused surgery and some are medically inoperable. These patients may be offered a course of external beam irradiation in addition to endocavitary therapy. The former may be delivered initially and, after 6–7 weeks, if significant regression of the tumour has been achieved, a short course of endocavitary irradiation is offered. While this combination of radiation techniques widens the scope for sphincter preservation, careful patient selection is imperative if the results are to continue to compete with those of surgery[9,14].

Since the inception of endocavitary irradiation at Highland Hospital 14 patients have presented with large villous adenomas. No invasive carcinoma was identified in any of these patients. The lesions were all greater than 3 cm in diameter and five had failed after treatment by numerous surgical manoeuvres. Owing to either medical inoperability or refusal of further surgery, these patients were referred to the Radiation Therapy department. It has been found that these tumours are more radioresistant than invasive adenocarcinoma, even when the unconventional fraction scheme of endocavitary irradiation is used, and higher doses are often required for eradication.

In 1983 a patient was referred for endocavitary irradiation with a rectal lesion which had metastasized to the liver. Histological examination of the tumour demonstrated carcinoid. The proctological examination revealed a grey exophytic lesion, quite unlike carcinoma in appearance. In an effort to avoid obstruction and a colostomy this patient was accepted for endocavitary irradiation with palliative intent. The tumour received 13000 cGy in four fractions over 71 days.

Results

At the time of the initial visit to the department, patients are accepted for either the radical (curative) or the palliative treatment group. Between July 1973 and June 1987, 192 patients were treated for cure. Local control has been achieved in 183 (95 per cent) patients (*Figures 2* and *3*). This is defined as no evidence of local disease on clinical examination or on laboratory or imaging studies. Nine patients have had local recurrence, three of whom have died of disease. Five of these nine patients were salvaged by surgery and one has persistent disease. Forty-five patients have died from intercurrent disease. Eighty patients have been followed for a minimum of 5 years. Cure was achieved in 74 (93 per cent) of these patients and two have died of disease.

Within the same time period (1973–1987), 117 patients

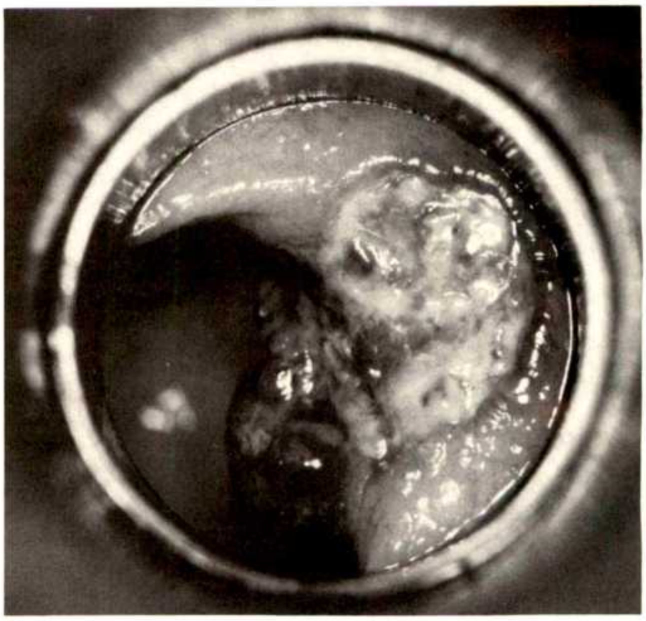


Figure 2 *Adenocarcinoma on rectal wall before endocavitary irradiation*

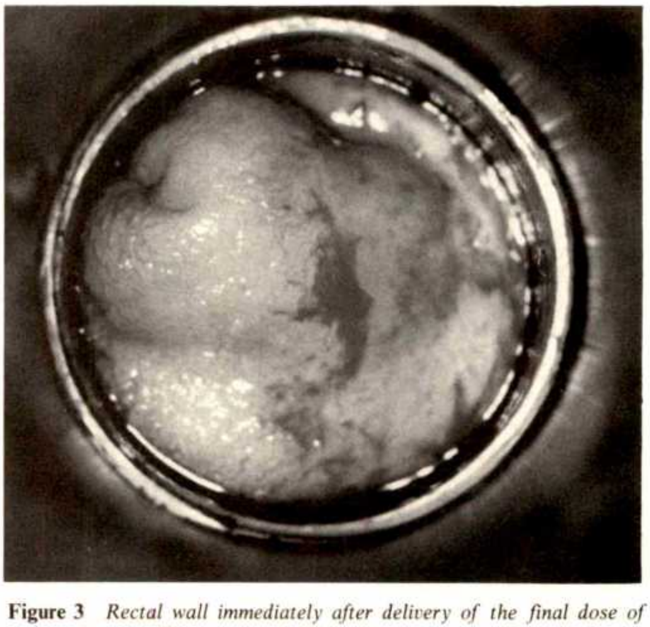


Figure 3 *Rectal wall immediately after delivery of the final dose of endocavitary irradiation (11 500 cGy in four treatments over 50 days)*

were assigned to the palliative group. In this group, 49 (42 per cent) patients appear to be cured in that they have not manifested recurrent disease to date; a further 51 patients (44 per cent) achieved significant palliation of symptoms; and 17 (14 per cent) patients received no discernible benefit from therapy.

Of the 14 patients who received treatment for villous adenomas, 4 have had local recurrence following endocavitary irradiation and were salvaged by a repeat course of therapy. Two of the four patients have died from other causes and two remain alive and well. Ten patients have required no further therapy.

The patient with a carcinoid tumour was observed carefully and after therapy moderate superficial necrosis was evident in the treatment area. Examination at 24 months revealed an increase in the size of liver metastases with the addition of mediastinal and bone involvement. He died of liver metastases 3·2 years after therapy; post-mortem examination revealed that the rectum was free of disease.

The mucosa of the rectum reacts remarkably well when subjected to the fractionation scheme used in endocavitary irradiation; following total doses as high as 17 500 cGy in six treatments over 100 days, sublethal damage is repaired. Over 400 patients have been thus treated at Highland Hospital and no serious local morbidity has been encountered although patients may experience minor bleeding or mucous discharge during the course of treatment. Of 403 patients 87 (22 per cent) have exhibited some superficial necrosis in the treatment area and healing has occurred after the use of steroid enemas. Long-term follow-up usually reveals an area of slight atrophy at the treatment site but otherwise the rectal wall is smooth and soft on palpation. Some patients demonstrate telangiectasia within the atrophic area and these patients may report minor bleeding following the ingestion of excessive roughage. A few patients have reported unusually persistent bleeding after treatment and it is interesting that on careful questioning a number of these patients admit to the use of routine aspirin for anticoagulation.

A number of patients are referred for endocavitary irradiation following unsuccessful attempts at local excision with or without fulguration. In some instances these procedures have been carried out on several occasions and the patient presents for endocavitary irradiation after more than one recurrence. The outcome of these patients after therapy is comparable to that of patients who have undergone a pretreatment biopsy, but the local reaction is considerably more pronounced. In the group of 192 patients treated for cure by endocavitary irradiation, 32 patients had undergone prior surgical procedures in addition to a biopsy. After treatment, excessive local reaction was demonstrated in 14 (44 per cent) of these patients. Superficial necrosis in the target area, although asymptomatic, may require protracted courses of steroid retention enemas before healing takes place. After surgical procedures the vasculature of the rectal mucosa is disturbed and tumour cells may be lodged in anoxic scar tissue, causing increased radioresistance.

Discussion

The modified squamous epithelium of the anal canal responds to irradiation in a manner similar to that of normal skin. It is crucial therefore that patients in whom the rectal lesion encroaches into the anal canal are not treated in this way. Some patients have been treated where the inferior border of the lesion was 0·25 cm above the dentate line. A few months after therapy, proctitis developed which eventually responded to steroid retention enemas. If the anal canal is treated the possibility exists that a very severe proctitis would develop, necessitating an abdominoperineal resection for pain control. After endocavitary irradiation many patients are followed not only in the radiation therapy department but also by their surgeon and/or endoscopist. This allows optimal follow-up as patients are able to undergo regular colonoscopy in addition to sigmoidoscopy. There is a tendency to view with suspicion the area of the rectal mucosa that has received treatment. In an effort to rule out local recurrence, post-treatment biopsies of mucosa with normal appearance are sometimes taken; subseqently a fibrotic nodule may be palpated, prompting further investigation which may include a second biopsy. At this time there appears to be a lack of understanding that tissue which has received high doses of irradiation heals by fibrosis and frequent biopsies may lead to unnecessary radical procedures, performed for suspected recurrence.

It has become apparent that the time–dose relationship of endocavitary irradiation is very important. It is felt that the optimal schedule is approximately four treatments within 60 days, given at intervals of 2–3 weeks; if additional doses are required, they should be given over a proportionate time. Three of nine patients in the curative group who had local recurrence received therapy over what is now considered an excessive time period. All three patients came from outside the community and experienced travel difficulties for a variety of reasons.

For three-quarters of a century surgery has been the traditional accepted management for all stages of carcinoma of the rectum. Radiotherapy is now challenging the role of surgery in the treatment of early disease. It is interesting that this should be accomplished by the peculiar use of a low energy beam machine which has been available for many years, rather than by one of the more powerful machines that takes advantage of new technology. It is regrettable that this machine is no longer in production.

References

1. Papillon J. *Rectal and Anal Cancers—Conservative Treatment by Irradiation—An Alternative to Radical Surgery*. New York: Springer-Verlag, 1982.
2. Axtell LM, Cutler SJ, Myers MH. End results in cancer. 1972; Report No. 4 HEW Publication (NIH): 173–272.
3. Morson BC. Factors influencing the progress of early cancer of the rectum. *Proc R Soc Med* 1966; **59**: 607–8.
4. Nicholls RJ. The clinical staging of rectal cancer. *Br J Surg* 1982; **69**: 404–9.
5. Beynon J, Roe AM, Foy DMA, Channer JL, Virjee J, Mortensen NJ McC. Preoperative staging of local invasion in rectal cancer using endoluminal ultrasound. *J R Soc Med* 1987; **80**: 23–4.
6. Thoeni RF, Moss AA, Schnyder P, Margulis AR. Detection and staging of primary rectal and rectosigmoid cancer by computed technology. *Radiology* 1981; **141**: 135–8.
7. Hodgeman CG, MacCarty RL, Wolff BG *et al.* Preoperative staging of rectal carcinoma by computed tomography and 0.15T magnetic resonance imaging. Preliminary report. *Dis Colon Rectum* 1986; **29**: 446–50.
8. Butch RJ, Stark DD, Wittenburg J. Staging rectal cancer by MR and CT. *AJR* 1986; **146**: 1155–60.
9. Papillon J. The future of external beam irradiation as initial treatment of rectal cancer. *Br J Surg* 1987; **74**: 449–54.
10. Higgins Jr GA, Conn JH, Jordan Jr PHJ, Humphrey EW, Roswit B, Keehn RJ. Pre-operative radiotherapy for colorectal cancer. *Ann Surg* 1975; **181**: 624–31.
11. Withers HR, Romsdahl M, Barkley HT *et al.* Post-op radiation therapy for rectal cancer. In: Salmon SE, Jones SE, eds. *Adjuvant Therapy of Cancer II*. New York: Grune & Stratton Inc, 1979: 621–8.
12. Pahlman L, Glimelius B, Graffman S. Pre- *versus* postoperative radiotherapy in rectal carcinoma: an interim report from a randomized multicentre trial. *Br J Surg* 1985; **72**: 961–6.
13. Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N. Final results of a randomized trial on the treatment of rectal cancer with pre-operative radiotherapy alone or in combination with 5-Fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer. Gastrointestinal Tract Cancer Cooperative Group. *Cancer* 1984; **53**: 1811–18.
14. Myerson RJ, Walz BJ, Kodner IJ *et al.* Endocavitary radiation for early rectal carcinomas: the experience at Washington University. (Abstract) *Int J Radiat Oncol Biol Phys* 1987; **13** (Suppl. 1): 194.

Paper accepted 11 April 1988

Br. J. Surg. 1988, Vol. 75, September, 904–905

An aetiology for fistula in ano

I. K. Pople and D. N. L. Ralphs

Department of Surgery, Norfolk and Norwich Hospital, Brunswick Road, Norwich, UK

Correspondence to:
Mr D. N. L. Ralphs

Four cases of superficial peri-anal fistula occurring in early infancy are described. They were all successfully treated by complete excision of the fistula. Histological examination of the excised fistulae revealed a mixture of columnar, transitional and stratified squamous epithelium lining the tracts in three cases and non-specific connective tissue in the fourth. It is postulated that the presence of these inappropriate types of epithelium (columnar and transitional) along the length of the fistulous tract is evidence of a congenital origin for peri-anal fistulae presenting in the first few months of life.

Keywords: Peri-anal fistula, congenital aetiology

It is generally considered that peri-anal fistulae arise as a result of preceding peri-anal sepsis. The origin of some abscesses from anal glands was postulated by Parks[1], who also proposed that fistulae found in early childhood were likely to be due to congenital abnormalities of these glands. To support the proposition that many fistulae of early childhood are of congenital origin we reviewed the case histories of four infants who presented to us with this problem over a period of 5 months.

Case reports

Case 1

A 13-month-old boy with a history of two previous peri-anal abscesses, one at 6 months and the other at 11 months, presented with a pit antero-lateral to the anus. At operation he was found to have a superficial (subcutaneous) peri-anal fistula (*Figure 1*) which was excised and submitted for histological examination. The fistula tract was lined partly by transitional-type epithelium and partly by inflamed granulation tissue (*Figure 2*).

Case 2

A 2-month-old boy presented with a persistent discharge from a small pit antero-lateral to the anus, which followed a peri-anal abscess 3 weeks previously. At operation a superficial peri-anal fistula was found and excised. Histological examination revealed columnar, mucus-secreting epithelium along the length of the tract with surrounding layers of squamous or transitional-type epithelium.

Case 3

A 5-month-old boy presented with a pit antero-lateral to the anus which had appeared after a peri-anal abscess had discharged its contents 4 weeks previously. Under anaesthetic, probing of the pit revealed a superficial peri-anal fistula which was completely excised and found to be lined partly by stratified squamous and partly by a layer of columnar cells superficial to several layers of proliferated 'reserve' cells.

Case 4

An 8-month-old boy was referred after two peri-anal abscesses had been drained 6 and 8 weeks previously. He had a small pit lateral to the anus, which was shown at operation to be part of a superficial peri-anal fistula. The histological features of the fistula tract were found to be non-specific.

In all four infants the wounds had healed completely within 1 week. None had recurred at review 10 months after operation.

Discussion

The four male infants all presented with a history of peri-anal abscesses, which in three had discharged spontaneously. In all cases the cutaneous opening was anterior to the anus and the tracts ran radially to the ano-rectum. All were superficial and, in three, there was no clinical evidence of infection at the time of presentation. The fistulae were treated conventionally by excision of the tract and laying open the wound. The results have been uniformly good with rapid healing.

The presence of transitional and columnar epithelium, which formed a substantial part of the lining of three of the fistulae, was not expected. There are two possible explanations for the presence of these epithelia. One is metaplasia due to chronic

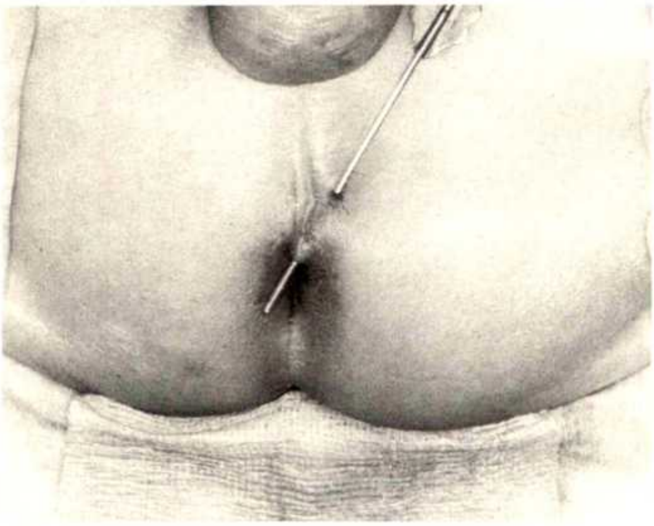


Figure 1 *Fistula* in ano *in 13-month-old boy*

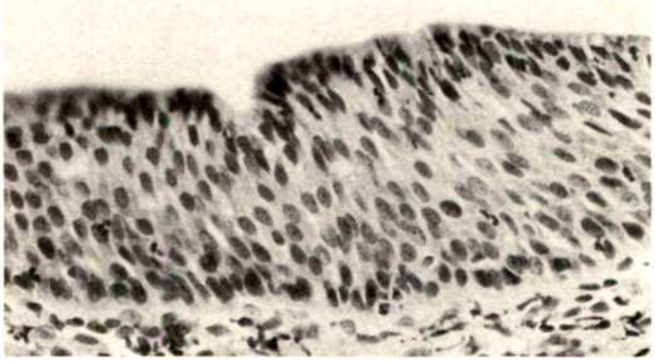


Figure 2 *Histological appearance of fistula tract showing well-organized transitional epithelium*

0007–1323/88/090904–02$3.00 © 1988 Butterworth & Co (Publishers) Ltd

inflammation. This inflammation is generally attributed in adults to infection within a peri-anal gland, leading to abscess and subsequent fistula formation[1]. More recently, it has been proposed that an excess of androgens may lead to the formation of abnormal anal glands *in utero* and that these are predisposed to infection[2,3].

In our cases, the extent and well ordered nature of the epithelial tract lining combined with the inconstant presence of inflammatory cell infiltrates on histology leads us to postulate an alternative explanation for the genesis of these fistulae in infants. It is known that ectopic epithelia can appear at a distance from their site of origin due to early migration of cells during development[4]. Given this potential, it would be surprising if during the early complex development of the perineum from the cloacal membrane, migratory cells from the urogenital sinus or the primitive hindgut did not, on occasion, become locally displaced.

The formation of the male perineum involves fusion of the urethral and genital folds over the urogenital sinus, which differentiates into the bladder and urethra. The migratory cells from the urogenital sinus could then become trapped amid the fused folds in the subcutaneous tissue of the peri-anal region and in close proximity to the anteriorly placed anal glands[5]. This might explain the higher incidence of peri-anal fistulae in males as the fusion of the genital folds in the female is much less extensive, and might also account for the fact that most of these tracts are anterior to a line drawn horizontally through the anus.

Congenital fistulae in the perineum due to failure of fusion of genital folds can occur, but are rare[6]. We suggest that, more commonly, congenital sinuses penetrate deep into the peri-anal tissues. Inflammation at the blind subcutaneous end of such a tract leads to suppuration and discharge through the skin with the establishment of a fistula. The predisposition to the condition is therefore primarily congenital. If it is accepted that many peri-anal fistulae of early childhood have this aetiology, then adult peri-anal fistulae may have a similar cause. In this circumstance, however, chronic inflammation leads to destruction of the well ordered ectopic epithelia giving rise to the standard theory that the fistulae are caused solely by infection.

Acknowledgements

We would like to thank Dr J. H. Rack for his help in providing the histological information

References

1. Parks AG. Pathogenesis and treatment of fistula-in-ano. *Br Med J* 1961; **1**: 463–9
2. Fitzgerald RJ, Harding B, Ryan W. Fistula-in-ano in childhood A congenital etiology. *J Ped Surg* 1985; **20**: 80–1.
3. Duhamel J. Anal fistulae in childhood *Am J Proctol* 1975; **26**: 40–3.
4. Parkask S, Veliath AJ, Chandrasekaran V Ectopic gastric mucosa in duplication of the rectum presenting as a peri-anal fistula *Dis Colon Rectum* 1982; **25**: 225–6.
5. Van-der Putte SCJ. Normal and abnormal development of the anorectum *J Ped Surg* 1986; **21**: 434–40.
6. Spitz L, Poong MJ Congenital H-type fistulae of the anorectal region. *Am J Proctol* 1980; **31**: 22–3

Paper accepted 12 April 1988

Br. J. Surg. 1988, Vol. 75, September, 906–909

Proliferation patterns and aneuploidy in adenomatous polyps of the colon

J. Matthews, S. Sousha*, R. A. Parkins†, M. Glynn† and T. Cooke‡

Departments of Surgery, Pathology and †Gastroenterology, Charing Cross and Westminster Medical School, London, and ‡Royal Liverpool Hospital, Liverpool, UK

Correspondence to: Mr T Cooke, Department of Surgery, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP, UK

The frequency of aneuploidy and the proliferative activity of 57 colorectal adenomatous polyps was investigated by static cytophotometry and compared with 43 adenocarcinomas and 60 samples of normal mucosa. Twenty per cent of the adenomas contained aneuploid cells compared with 63 per cent of the adenocarcinomas. Except in the case of villous adenomas, there was a general increase in the proliferative activity of the diploid adenomas with increasing degrees of dysplasia. All of the adenomas showed an increase in proliferation compared with normal mucosa. There was a positive correlation between the size of the diploid adenomas and proliferative activity ($P<0.001$).

Keywords: Cell proliferation, ploidy, colonic adenomas

Large bowel adenomas are common lesions in those populations where there is a high incidence of colorectal cancer[1] and some of these adenomas will be the precursors of malignant neoplasms. The likelihood of malignancy developing in an adenoma is related to increasing size, a villous as opposed to a tubular growth pattern, and the severity of dysplasia of the epithelium[2]. The interpretation of dysplasia, however, is a subjective assessment with disagreement between pathologists which reduces its use in predicting malignant change.

It is known that some colonic carcinomas contain aneuploid cell lines[3] so the presence of these aneuploid cells in adenomatous polyps may be indicative of malignant change. Aneuploid cells would not be expected in adenomas that are going to develop into diploid adenocarcinomas, so this test would not predict malignant change in diploid adenomas. It is probable that as adenomas undergo malignant change, there is an alteration in the kinetic organization of the cells. This paper investigates the proliferative activity of adenomatous polyps in an attempt to distinguish those polyps which are most likely to undergo malignant change.

Materials and methods

A total of 57 adenomatous polyps were investigated either after removal by diathermy at colonoscopy or after surgical resection. The polyps were measured and the surface was brushed vigorously with a cytological brush yielding single cells which were suspended in Hanks' tissue culture medium containing 10 per cent ethanol and 1 per cent glacial acetic acid. The polyps were fixed in formalin for histological examination and examined by an independent histopathologist experienced in the interpretation of colonic pathology. Material from 43 large bowel carcinomas, and from 60 samples of normal mucosa taken at colonoscopy from patients without neoplastic disease or inflammatory disease at different sites on the colon, were also investigated for comparison.

The cell samples were syringed through a 25G needle three times to disaggregate any clumps of cells. The cells were then washed three times in PBS pH 7·4 and cytopreparations were made using a Shandon* cytospin and these were then fixed in Carbowax* ethanol containing 1 per cent glacial acetic acid and 0·3 per cent polyethylene glycol).

Histochemistry

After being hydrolysed for 50 min in 5N hydrochloric acid, the cells were stained for DNA with Schiff's reagent.

DNA measurement

Measurements were made by means of a Vickers M85 scanning and integrating microdensitometer at 550 nm with a ×40 objective and a scanning spot size of 0·5 μm in the plane of the specimen. A mask which had a diameter of either 10, 15 or 20 μm was used depending on the size of the cells in the sample. The DNA content of 100 epithelial cells was measured, cells being selected using a grid system on a manually operated stage to prevent any bias. Histograms of DNA content were plotted and the percentage of cells containing a hyperdiploid DNA content was calculated and this was called the proliferative index. After the DNA content of 100 cells had been measured for the proliferative index, the whole slide containing up to 2000 cells was scanned for the presence of hyperchromic cells and those with large nuclei. The DNA content of these cells was measured and the presence of any containing a hypertetraploid DNA content was noted.

Statistics

The proliferative indices and the size of diploid and aneuploid adenomas were compared using Student's *t* test. No statistical analysis has been attempted to compare the ploidy profiles because of the small numbers of adenomas in the different subsets. Linear regression analysis was used to correlate the size of the diploid adenomas with the proliferative indices.

Results

Histological assessment

Of the 57 adenomatous polyps, 38 were tubular adenomas, 15 were tubulovillous adenomas and 4 were villous adenomas. Of the 38 tubular adenomas, 12 had mild dysplasia, 25 had moderate dysplasia and 1 had severe dysplasia. Of the 15 tubulovillous adenomas, 5 had mild dysplasia, 7 had moderate dysplasia and 3 had severe dysplasia. Two of the villous adenomas had moderate dysplasia and two had severe dysplasia.

Ploidy profiles

Four types of ploidy histograms were obtained for the adenomas and the adenocarcinomas. The first type showed a single diploid peak, with an even number of cells between diploid and tetraploid (*Figure 1*). In type 2 there was a diploid peak and a second smaller tetraploid peak with a small number of cells in between. The third type showed a similar pattern to types 1 and 2, but with additional cells containing a hypertetraploid DNA content, and in the fourth type a second peak not in the tetraploid range, as well as hypertetraploid cells were seen (*Figure 1*). Type 3 and type 4 histograms were classified as aneuploid.

All specimens of normal mucosa had DNA histograms with the type 1 diploid profile. The distribution of the ploidy profiles of the adenomas and adenocarcinomas, and the relationship of the ploidy profiles with histological type and degree of dysplasia of the adenomas is summarized in *Table 1*. Thirteen per cent of the tubular adenomas were aneuploid. This is increased to

---

* *Carbowax is manufactured by Sigma Chemical Company Ltd., Poole, UK. Shandon cytospin is manufactured by Shandon Southern Products Ltd, Runcorn, UK*

33 per cent in the tubulovillous adenomas and again to 50 per cent in the villous adenomas. Aneuploidy was seen more frequently in the adenomas with moderate or severe dysplasia than in those with mild dysplasia, although the degree of differentiation of the adenocarcinomas did not show any correlation with the percentage of aneuploid lesions. In total, 21 per cent of the adenomas contained aneuploid cells compared with 63 per cent of the adenocarcinomas.

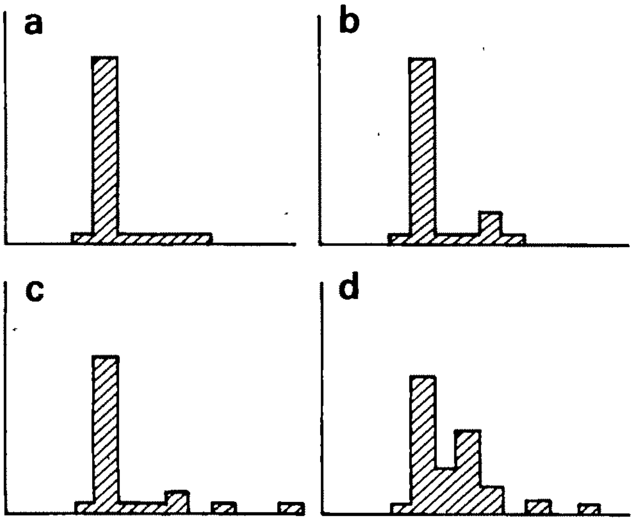


Figure 1 *DNA distribution patterns of the four types of profiles seen.* **a** *type 1;* **b** *type 2,* **c** *type 3,* **d** *type 4*

Relationship of ploidy to size

The mean size of the aneuploid adenomas was 2·3±0·6 cm which was significantly larger than the mean size of the diploid adenomas (1·1±0·14 cm, $P < 0·02$).

Proliferative indices

Relationship to adenoma type. The mean proliferative index of normal mucosa (2·2±0·3) was significantly lower than the mean values of the diploid adenomas (9·6±0·8) and the diploid carcinomas (17·7±2·4) ($P < 0·001$). The mean values obtained for the' tubular adenomas (9·0±0·9) and the tubulovillous adenomas (12·7±2·1) were not significantly different although both of these values were significantly higher than that of normal mucosa ($P < 0·001$). The two diploid villous adenomas studied had a mean proliferative index of 4·5±1·5, which was lower than the other adenomas and not significantly different from normal mucosa. Overall, the adenomas had significantly lower proliferative indices than the adenocarcinomas ($P < 0·001$).

Relationship to degree of dysplasia. The mean proliferative index of 6·5±1·1 in the diploid adenomas with minimal dysplasia was significantly lower than the mean proliferative index of 11·7±1·1 in the diploid adenomas with moderate dysplasia ($P < 0·01$) (*Table 2*), although the value for the lesions with mild dysplasia was still significantly greater than the value obtained for normal mucosa ($P < 0·001$). The mean proliferative index in adenomas with severe dysplasia of 11·0±3·8 was not significantly different from those with mild or moderate dysplasia although there were only four specimens in the group.

The diploid carcinomas contained significantly more proliferating cells than the diploid tubular adenomas with mild

Table 1 *Ploidy profiles of the different types of adenomas, compared with adenocarcinomas and normal mucosa*

				Ploidy profile			
	n	Degree of dysplasia	*n*	Type 1	Type 2	Type 3	Type 4
Tubular adenomas	38	Mild	12	11 (92%)	1 (8%)	0	0
		Moderate	25	16 (64%)	4 (16%)	5 (20%)	0
		Severe	1	0	1 (100%)	0	0
		Total		27 (71%)	6 (16%)	5 (13%)	0
Tubulovillous adenomas	15	Mild	5	3 (60%)	1 (20%)	0	1 (20%)
		Moderate	7	3 (43%)	2 (29%)	2 (29%)	0
		Severe,	3	0	1 (33%)	1 (33%)	1 (33%)
		Total		6 (40%)	4 (27%)	3 (20%)	2 (13%)
Villous adenomas	4	Mild	0	0	0	0	0
		Moderate	2	0	0	1 (50%)	1 (50%)
		Severe	2	2 (100%)	0	0	0
		Total		2 (50%)	0	1 (25%)	1 (25%)
Adenocarcinomas	43	Well	3	1 (33%)	0	0	2 (67%)
		Moderate	35	7 (20%)	6 (17%)	3 (9%)	19 (54%)
		Poor	5	1 (20%)	1 (20%)	1 (20%)	2 (40%)
		Total		9 (21%)	7 (16%)	4 (9%)	23 (53%)
Normal mucosa	60			60 (100%)	0	0	0

Table 2 *Proliferative indices of the different types of diploid adenomas ±s.e.m. compared with diploid adenocarcinomas and normal mucosa*

	Degree of dysplasia							
	Mild	Moderate	Severe	Total	Well differentiated	Moderate	Poor	Total
Tubular adenomas	5·8±1·3	10·6±0·9	17	9·0±0·9				
Tubulovillous adenomas	8·8±2·1	14·8±3·5	18	12·7±2·1				
Villous adenomas	—	—	4·5±1·5	4·5±1·5				
Total	6·5±1·1	11·7±1·1	11·0±3·8	9·6±0·8				
Adenocarcinomas					5	19·3±2·7	14·5±1·5	17·7±2·4
Normal mucosa					2·2±0·3	—	—	2·2±0·3

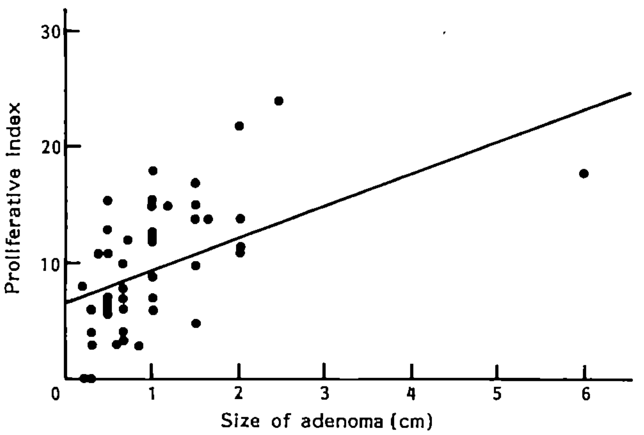


Figure 2 *Graph showing correlation of size of diploid adenomas with proliferative index* ($r=0{\cdot}56$, $P<0{\cdot}001$)

or moderate dysplasia ($P<0{\cdot}001$ and $P<0{\cdot}01$ respectively) and the villous adenomas with severe dysplasia. There was no significant difference in the number of proliferating cells in the diploid cancers, the tubular adenomas with severe dysplasia, and the tubulovillous adenomas with moderate or severe dysplasia.

Relationship to size. There was a positive correlation between size and proliferative index of the diploid adenomas ($r=0{\cdot}56$, $P<0{\cdot}001$) (*Figure 2*).

Discussion

There are three methods available for obtaining cells for cytometry. These are enzymatic or mechanical disaggregation of fresh tissue, enzymatic disaggregation of paraffin wax embedded material, and the method described in this study. Unless the whole lesion is disaggregated, all of these techniques have sampling errors. Because the main aim of this study was to look at cell proliferation rather than aneuploidy as such, the use of cytological brushes to obtain cells is probably the technique that produces the most relevant results. In normal mucosa, it has been shown[4] that cytological brushing liberates cells from the upper parts of the crypts where little, if any, proliferative activity is seen and is reflected in the low proliferative indices obtained in our normal mucosa. In polyps there is a shift in proliferative activity to the upper parts of the crypts with over 60 per cent of cells undergoing DNA synthesis being located in the upper third of the neoplastic glands[5]. This shift can be detected when brushes are used to liberate the cells from the adenomas whereas disaggregation of whole lesions would not produce any information on the location of the proliferating cells. We have previously reported a comparison between this technique and the crypt cell production rate, an established measurement of colonic mucosal kinetics, and found a good correlation[6].

This study agrees with previous findings from both ploidy and cytogenic studies that some adenomas contain aneuploid cells[7-9]. In this study, the presence of aneuploid cells in the adenomas was not necessarily related to severe dysplasia, with 9 of the 12 aneuploid lesions being associated with moderate dysplasia. Of the other three aneuploid lesions, one had mild dysplasia and two had severe dysplasia. Since there is a well recognized discrepancy in the interpretation of dysplasia between histopathologists, the presence of aneuploid cells within the polyps may be a better indicator of malignant potential than pathological assessment. Only three of the adenomas that contained aneuploid cells had a type 4 ploidy profile, i.e. with a hyperdiploid peak that was not in the tetraploid range, as well as containing hypertetraploid cells, whereas 23 of the 27 aneuploid adenocarcinomas had type 4 ploidy profiles. This is probably a reflection of the small numbers of aneuploid cells present in the adenomas as a proportion of the whole lesion compared with adenocarcinomas, rather than a true difference between the adenomas and adenocarcinomas.

Although the presence of aneuploidy in adenomas is probably the best indicator of malignant potential, only 63 per cent of the adenocarcinomas in this study contained aneuploid cells. It is not likely that a precursor of a diploid tumour will be aneuploid so other parameters are required for diploid adenomas to assess their malignant potential. Of the 45 diploid adenomas studied 35 had a type 1 ploidy profile, i.e. with a main peak at diploid with hyperdiploid cells evenly distributed between diploid and tetraploid, while the other 10 had a type 2 ploidy profile, with an obvious tetraploid peak. The diploid adenocarcinomas were equally distributed between type 1 and type 2 profiles.

Interpretation of tetraploid peaks in ploidy profiles is not easy, as it is impossible using this technique to distinguish aneuploid cells with a tetraploid DNA content from cells that are in the G_2 or mitotic phases of the cell cycle. If it is assumed that aneuploid cells divide and are not end cells then, if tetraploid cells are aneuploid, the cells in G_2 or M will contain a hypertetraploid DNA content. For this reason, the cells in the tetraploid peaks of a type 2 profile were assumed to be dividing diploid cells. The presence or absence of a tetraploid peak in a diploid profile is an indicator of the length of time the cells are in each part of the cell cycle. If the cells have a long G_2 phase, then a tetraploid peak would be expected. Since type 1 and type 2 profiles were found in both the adenomas and adenocarcinomas, it is unlikely that the type of diploid profile of adenomas is an indicator of malignant potential. All of the samples of normal mucosa showed a type 1 ploidy profile, so there has been a transformation in the kinetic activity in the adenomas with a type 2 profile. However, the relevance of this is not clear.

Attempts have been made to assess proliferative indices of adenomas using flow cytometry[4]. Although an increase was seen in the proliferative activity of adenomas with severe dysplasia, the results were not necessarily accurate as this technique does not distinguish the different cell types in the sample. The static method of DNA assessment used in this study allows each cell that is measured to be identified so that an accurate proliferative index can be produced.

The proliferative index of aneuploid tumours, benign or malignant, could not be assessed because it was impossible to distinguish between aneuploid cells and cells that were in the S, G_2 or mitotic phases of the cell cycle. The diploid adenomatous polyps in this study which showed a moderate degree of dysplasia had a significantly higher degree of proliferative activity than those with a mild degree of dysplasia. There were not enough diploid adenomas with severe dysplasia for a meaningful comparison to be made with the other groups, although the values obtained for the two villous adenomas with severe dysplasia were surprisingly low. Both of these villous adenomas were small (0·5 cm and 0·6 cm) which may account for the low proliferative activity, but it is more likely that because of the histological structure of villous adenomas, cells are only being released from the villi where a high level of proliferative activity would not be expected. If this is the case, an alternative method of obtaining single cells from throughout the lesion would need to be used. If the results from the villous adenomas are omitted, the mean proliferative index of the other diploid adenomas with severe dysplasia was 50 per cent higher than the mean value obtained for the adenomas with moderate dysplasia. Although there were no significant differences in the proliferative indices of the tubular and tubulovillous adenomas, there was a trend for the tubulovillous adenomas, which are known to have a greater risk of malignancy than tubular adenomas[2], to have higher proliferative indices than the tubular adenomas. This was the case with lesions with mild, moderate and severe dysplasia. The diploid adenocarcinomas had a proliferative index significantly higher than the values obtained for the adenomas with mild or moderate dysplasia, but similar to the value obtained for the tubular and tubulovillous adenomas with severe dysplasia. These results would suggest that the proliferative index increases as a lesion develops a greater malignant potential. An increase in the numbers of dividing cells, especially when those cells are in contact with the faecal stream and any carcinogens contained within it, as is the case in adenomas, will increase the probability of a mutation resulting in malignant transformation.

In a study from St. Mark's Hospital, adenomas less than 1 cm in diameter had a malignancy rate of 1·3 per cent, those between 1 cm and 2 cm a rate of 9·5 per cent, and those over 2 cm a rate of 46 per cent[2]. In this study a positive correlation was found between size of adenomas and their proliferative index, adding further support to the hypothesis that an adenoma with a high proliferative index is at greater risk of becoming malignant than one with a low proliferative index.

References

1. Day DW The adenoma–carcinoma sequence. *Scan J Gastroenterol* 1984; **19** (Suppl 104). 99–107.
2 Muto T, Bussey HJR, Morson BC. The evaluation of cancer of the colon and rectum. *Cancer* 1975; **36**· 2251–70.
3. Wolley RC, Schreiber K, Kass LG, Karas M, Sherman A. DNA distribution in human colon carcinomas and its relationship to clinical behaviour. *J Nat Cancer Inst* 1982, **69**: 15–22
4. Matthews J, Glynn M, Parkins A, Cooke T Alteration in colonic epithelial cell DNA associated with intestinal neoplasia selection of high risk patients. *Br J Surg* 1987, **74**: 23–5.
5 Deschner EE. Adenomas· preneoplastic events, growth and development in man and experimental systems *Pathol Ann* 1983, **18**· 205–19.
6. Strachan JR, Matthews J, Rees HC, Cooke T. Kinetic changes in experimental colonic urinary diversion. *Br J Surg* 1987; **74**: 1046–8
7. Weiss H, Wildner GP, Jacobasch KH, Heinz U, Schaeliche W Charactensation of human adenomatous polyps of the colorectal bowel by means of DNS distribution patterns *Oncology* 1985; **42** 33–41
8. Baker MC, Atkin NB. Chromosome abnormalities in polyps and carcinomas of the large bowel. *Proc R Soc Med* 1970, **63**· 9–10.
9 Enterline HT, Arvan DA. Chromosome constitution of adenoma and adenocarcinoma of the colon. *Cancer* 1967; **20**· 1746–59

Paper accepted 10 April 1988

Br. J. Surg. 1988, Vol. 75, September, 910–912

Villous tumours of the large bowel

S. G. Pollard,
R. Macfarlane and
W. G. Everett

Department of Surgery, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK
Correspondence to:
Mr S G. Pollard

A series of 110 patients with villous tumours of the colon and rectum treated by a single surgeon over an 18-year period is reported. Multiple lesions were present in 15 per cent of patients and 24 per cent of cases contained invasive malignancy, of which 83 per cent were Dukes' A. The major lesion was in the rectum in 84 per cent of patients and in the sigmoid colon in 12 per cent. Rectal bleeding and diarrhoea were the most common presenting symptoms; 6 per cent of patients were asymptomatic. Digital assessment proved a more reliable indicator of the presence of malignancy than either random biopsy or barium enema. In all, 70 of 76 (92 per cent) benign rectal lesions and 15 of 22 (68 per cent) malignant rectal lesions were successfully removed by peranal submucous excision or snaring and none of the malignancies so treated has developed a recurrence to date. Benign recurrence has developed in 13 per cent of all patients; the majority appeared within 4 years and were at the same level as the initial lesion. Of the 79 patients with benign tumours 7·6 per cent have subsequently developed large bowel carcinomas, after 2–16 years; all were symptomatic, half were at the same level as the previous benign lesion, and half were suitable for peranal removal.

Keywords: Villous adenoma, rectal polyp, colorectal carcinoma, peranal submucous resection

The first clinical description of a villous tumour of the colon was made by Holmes in 1861[1], and their propensity to undergo malignant transformation is now well recognized. Despite advances in peranal surgery, there remains a tendency among surgeons to submit patients with villous tumours of the rectum which are benign but extensive, or contain foci of malignancy, to anterior resection or abdominoperineal excision of the rectum. We have demonstrated that it should rarely be necessary to resort to such measures since the majority of villous tumours, both benign and malignant, can be removed through the anus under a light general anaesthetic with minimal upset to the patient, and without incurring unacceptable rates of local recurrence.

Patients and methods

The case notes of patients with villous tumours of the large bowel referred to a single surgeon (W.G.E.) have been reviewed retrospectively. From 1969 to 1987, 110 consecutive patients have been treated. Small tumours avulsed via the sigmoidoscope in the outpatient clinic have not been included. The data were obtained from personal records of cases treated, cross-checked by pathological reports. The patients were referred by physicians or general practitioners, and not by other surgeons requesting a particular operative procedure. There were 55 men and 55 women with a mean age of 69 years (range 37–96).

The villous adenoma was an incidental finding during colonic resection for carcinoma in five cases, and one further villous adenoma was resected during a colectomy for Crohn's disease. These cases will not be considered further. Of the remaining 104 patients the tumour was situated in the rectum in 87 (84 per cent). Thirteen had lesions in the sigmoid (12 per cent). In only four patients were the tumours situated more proximally in the colon (4 per cent).

The incidence of symptoms is listed in *Table 1*. Only six patients were asymptomatic (6 per cent), and there was no difference in symptomatology between benign and malignant lesions. Digital assessment was possible in 53 rectal lesions (51 per cent of total with villous adenomas), of which 42 were benign. All 11 malignant tumours were correctly assessed, but one benign lesion was misdiagnosed as malignant.

Pre-operative barium enema was performed in 82 of the 104 patients, of whom 64 had benign tumours and 18 malignant. The correct diagnosis was made in 46 cases (56 per cent), of which 39 were benign and 7 malignant. Misdiagnosis occurred in 14 (17 per cent): 11 benign lesions (average size 6 cm, all sessile) and 3 malignant ones (average size 4 cm, 2 sessile and one pedunculated). A further 10 (12 per cent) were reported as equivocal (5 benign, 5 malignant, all sessile; average size 4·5 cm). The lesion was missed entirely in 12 (15 per cent), of which 3 were malignant. The average distance from the anal canal in this group was 9 cm (range 3–15 cm) and the average size was 3 cm (range 1–5 cm). Three were pedunculated and the remainder sessile.

Colonoscopy was performed in seven patients. Four were correctly interpreted as benign, one was misinterpreted as malignant, and two lesions were missed (one in the rectum and one in the sigmoid colon).

Of the 87 patients with rectal tumours, 12 (14 per cent) had other, smaller lesions elsewhere in the large bowel (mean 2·3 lesions; range 2–5). Eleven of these lesions were in the rectum: the total number of rectal villous tumours was thus 98, of which 22 had undergone malignant change; 18 were Dukes' A (82 per cent), and 4 were Dukes' B (18 per cent). The size of malignant tumours ranged from 2·5 to 7 cm (mean 4 cm). Pre-operative biopsy was obtained in 17 of the 22 with malignancy but was positive in only 4 (24 per cent), even though 7 patients had more than 3 tissue samples taken. Multiple biopsies did not improve diagnostic accuracy. The distribution of the tumours is detailed in *Table 2*.

There were 13 patients with solitary sigmoid lesions, and a further 4 with synchronous rectal villous adenomas, making a total of 17. The only case of malignancy was one Dukes' A carcinoma (3 cm diameter), and this was correctly diagnosed by pre-operative biopsy, as were all five benign lesions sampled.

Of the four patients with more proximal lesions, three had large (>4 cm) sessile tumours and one had three polypoid villous adenomas in the transverse and descending colon. Of these, one of the multiple polyps and a 6 cm caecal lesion contained malignancy.

Peranal submucous resection was performed in 51 cases of rectal villous adenoma (42 per cent of all villous adenomas). The largest lesion removed in this way was 12 cm in length, and the maximum distance from the anal margin reached was 18 cm. Malignancy was found in 14

Table 1 *Symptoms arising from villous adenomas*

Rectal bleeding	64%
Diarrhoea	50%
Mucus per rectum	34%
Pain	11%
Prolapse	10%
Tenesmus	8%
Flatulence	7%
Symptomatic anaemia	6%
Urgency of defaecation	1%

Table 2 *Distribution of lesions in the rectum and sigmoid*

Site	No	Average size (cm)	Range (cm)
Sigmoid	17	3·1	1–6
Rectum			
Upper third	36	3·8	1–11
Middle third	36	5·1	1·5–17
Lower third	26	3·8	1 5–10

Level taken as midpoint of lesion

lesions and, of these, removal was considered to be histologically complete in 11; a full-thickness local excision was then performed in 1 patient, and anterior resection in the other 2. After peranal submucous resection, mucosal continuity was restored by direct suture for small defects, but imbrication of the underlying muscle was only undertaken for annular lesions. Large mucosal defects were left open.

Endoscopic snaring or Goodsall's ligature was employed in 37 rectal villous adenomas and 13 of the sigmoid lesions (41 per cent) of all villous adenomas); 4 of the rectal lesions contained malignancy, and 1 was histologically incomplete and was removed by anterior resection Of the remaining rectal cases, two large benign villous adenomas were excised by anterior resection and a further two by combined peranal submucous resection and colo-anal anastomosis Early in the series a York Mason trans-sphincteric approach was used for two benign tumours, but in retrospect both would now have been treated by peranal submucous resection. Four malignancies were treated by anterior resection· two of these followed submucous resection and one followed endoscopic polypectomy where excision had been incomplete. Three malignancies required abdominoperineal excision. The remaining four sigmoid villous adenomas, including the malignant lesion, were removed by sigmoid colectomy

The lesions proximal to the sigmoid colon (four patients) were all removed at laparotomy.

Results

Inadequate excision of malignant lesions occurred in three patients; one after snaring and two after peranal submucous resection. All three underwent colonic resection. Complications developed in five patients undergoing peranal submucous resection. Two elderly male patients suffered urinary retention, and one patient was returned to theatre for bleeding. One patient developed transient septicaemia. There was one case of stricture formation which followed excision of a sessile annular lesion and this responded satisfactorily to regular dilatation. Diathermy snaring resulted in one case of sigmoid perforation which necessitated colonic resection.

The period of follow-up ranges from 6 months to 18 years (mean 5·5 years). Benign recurrence has developed in 14 patients (13 per cent), of which 7 have been multiple (range 2–5). Solitary recurrences were found a mean of 2·5 years after surgery (range 1–8 years), and only 1 occurred at a different level from the original tumour (5 rectum, 2 sigmoid). All except 1 of the multiple recurrences first appeared within 4 years, and half were at the same level as before. All benign recurrences were treated by peranal submucous resection or snaring.

None of the 25 patients who had a malignant lesion excised has to date suffered a recurrence, either benign or malignant, over a mean period of 4·1 years (range 6 months–11 years). However, six patients who had initially benign lesions removed have since developed large bowel carcinomas (7·6 per cent) over a period of 2–16 years. Five were in the rectum with three at the same level as the initial resection. All five patients were symptomatic, passing blood or mucus per rectum, and all the lesions were less than 5 cm across. Three were Dukes' A and were removed by peranal submucous exision. The other two lesions, both Dukes' B, were treated by resection of the rectum. The sixth patient developed a carcinoma of the caecum 16 years after peranal resection of a benign villous adenoma of the rectum. This patient had been discharged from follow-up and presented with iron deficiency anaemia caused by a large Dukes' C_2 tumour. Four patients, none of whom developed recurrent villous adenomas, have subsequently developed tubular adenomas of the colon, all of which have been removed by snaring.

Discussion

Although villous adenomas may occasionally affect the stomach, duodenum, jejunum, ileum or appendix[2,3], the overwhelming majority are found in the large bowel, with around 75 per cent of these occurring in the rectum[4]. In all, 97 per cent are within 30 cm of the anus[5], and villous adenomas account for 5 per cent of all colonic tumours[4]. While some authors have found a predominance in the lower rectum, this has not been our experience, nor that of others who have found an equal distribution throughout the rectum[5]. We found synchronous colonic lesions, either benign or malignant, in 16 per cent of cases.

Villous adenomas have a definite malignant potential; sessile lesions are more likely to be malignant than pedunculated ones[6]. The likelihood of malignancy correlates with size of tumour in most series[7], although size alone is of little prognostic significance since 17 per cent of lesions less than 1·5 cm contain invasive tumour[8]. In our series invasive carcinoma occurred in 24 per cent of cases, and six malignancies (25 per cent) were 3 cm or less.

It is uncertain whether recurrence is primarily the result of incomplete excision, or of a field change in the neighbouring mucosa. The former is supported by the observation that almost all recurrences occur within a few years of surgery, and sessile lesions are more prone to recurrence than those with pedicles[9] However, the high incidence of synchronous and metachronous lesions support the field change theory.

Diarrhoea and the passage of blood or mucus per rectum are the usual presenting symptoms but about 25 per cent of patients are said to be asymptomatic at the time of diagnosis[8]. We found no correlation between symptoms and the presence of malignancy and only 6 per cent were asymptomatic. Electrolyte disturbance, although greatly emphasized, is found to be symptomatic in less than 1 per cent[7]. Four of our patients had hypokalaemia but in none was this severe, or symptomatic.

Because malignancy is frequently focal, random sampling is unreliable, although in one published series, where tissue sampling was directed to clinically suspicious areas, the accuracy of pre-operative biopsy was improved to 97 per cent[10]. Despite multiple biopsies, our false negative rate was 76 per cent. In contrast, digital examination was almost 100 per cent accurate, malignancy being indicated by the presence of induration, ulceration, or the inability to move the lesion over the underlying muscularis mucosa. Slight caution is needed since induration will follow fulguration[11] We found barium enema to be relatively unreliable, providing the correct diagnosis in only 56 per cent of cases. It should be pointed out that the X-rays have not been reviewed, and that the original examinations were performed by a variety of radiologists of different grades. Particular difficulty was experienced in predicting malignancy in large sessile lesions. The importance of sigmoidoscopy before radiology is underlined by the 15 per cent of rectal lesions that were missed entirely by barium enema.

Small polypoid lesions are readily treated by diathermy snare. Larger polyps may be prolapsed through the anus and excised after transfixion of the base with a Goodsall ligature. Although fulguration can be employed for sessile lesions, this is not an ideal treatment because of the high incidence of recurrence, the lack of histological material, and the risk of stricture formation if the lesion occupies more than 50 per cent of the bowel circumference[12]. Sessile lesions in low to mid-rectum may be prolapsed through the anus and excised along the line of the pseudopedicle created by traction[13,14].

In an attempt to gain access to the lower rectum without recourse to abdominoperineal excision or anterior resection, Kraske[15] in 1885 described a posterior approach lateral to the sacrum. York Mason subsequently described a trans-sphincteric route[16]. Although popular for a time, and employed twice early in this series, fistula formation (20 per cent) and incontinence may be serious complications[17], and both operations have been superseded by the peranal submucous excision described by Soave in 1964[18] and modified by Parks and Stuart[19]. There is evidence that local recurrence is less common following submucous resection than snaring with a diathermy loop[20].

We consider the operation of choice for low sessile or polypoid villous adenomas of the rectum is peranal submucous excision. Using a Parks' retractor and a headlamp the submucosa is infiltrated with dilute adrenaline solution and the tumour is dissected off the underlying muscle with diathermy. Tumours that arise close to the anorectal junction and extend for a considerable distance proximally can still be dealt with by submucous excision by starting the dissection at the lower margin of the lesion and pulling it down towards the operator as the dissection is continued. In this way extensive and high tumours can be removed. In our series the highest level achieved by this method was 18 cm and the largest lesion removed measured 12 cm. Even with very large villous adenomas a trial removal by submucous excision is worthwhile since nothing is lost if it proves impossible.

In one patient with a large circumferential villous adenoma the rectal wall was divided while attempting peranal submucous resection. The incision was therefore continued around the circumference of the bowel below the tumour, the villous adenoma was prolapsed through the anus; it was excised, and a peranal colo-anal anastomosis performed. This is an approach that could be considered in large rectal tumours when peranal submucous resection fails.

Difficulty in separating mucosa from the muscularis propria usually indicates the presence of local invasion and in these circumstances the full thickness of the bowel wall should be excised and the defect repaired. Previous excisional surgery, fulguration or biopsy can produce adherence and the surgeon may be unable to decide whether local invasion is present or not. It can therefore be argued that multiple random biopsies should be avoided, particularly in view of their inaccuracy, and a case can be made for excision without prior biopsy. Imbrication of the underlying muscle allows restoration of mucosal continuity, although we have found this unsatisfactory for large asymmetric lesions where the mucosa of the uninvolved side becomes unacceptably distorted and impinges upon the lumen of the rectum. Large areas of bare rectum epithelialize rapidly and rarely result in stricture formation. We have had only one case of secondary haemorrhage from denuded muscle.

The treatment of villous adenomas containing early invasive cancer is controversial. Until relatively recently major colonic resection was advocated, if necessary by abdominoperineal excision. Yet the probability of lymph node metastasis in the case of a tumour confined to the mucosa or submucosa is between 6 and 10 per cent, and most of these tumours will be poorly differentiated[21–23].

In our experience, peranal resection of early carcinomas is a safe and effective form of treatment providing resection appears histologically to be complete. We have found it uncommon to have to resort to a more major procedure, and when this has been necessary the local resection in no way interfered with subsequent surgery. We would therefore recommend this conservative approach, particularly in elderly or poor risk patients with low rectal tumours. Indeed, in our experience malignant tumours arising in villous adenomas have a favourable outlook, possibly because they are generally well differentiated, and often detected early. None of the 25 patients who had a malignant lesion has suffered a recurrence to date.

The benign recurrence rate in our series was 13 per cent, and the commonest site was the area of previous excision. Because almost all occurred within 4 years, follow-up should be most rigorous during this period, with particular attention to the level of previous resection. However, longer term review is advisable because of the risk of development of further large bowel polyps (13 per cent), or of metachronous carcinomas which occurred in 7·6 per cent of patients over a period of 2–16 years.

References

1 Holmes T. Villous tumours of the rectum. *Trans Pathol Soc Lond* 1861; **12** 120–1.

2. Kutin ND, Ranson JHC, Gouge TH, Localio SA Villous tumours of the duodenum. *Ann Surg* 1975, **181**· 164–8.

3. Hopkins GB. Villous adenoma and adenocarcinoma of the vermiform appendix· report of a case *Dis Colon Rectum* 1972; **15**: 461.

4. Scoma JA Management of benign villous adenomas of the entire rectum. *Dis Colon Rectum* 1978; **21**: 630–2.

5. Southwood WFW. Villous tumours of the large intestine: their pathogenesis, symptomatology, diagnosis and management. *Ann R Coll Surg Engl* 1962; **30**: 23–45

6. Wilcox GM, Anderson PB, Colacchio TA. Early invasive carcinoma in colonic polyps A review of the literature with emphasis on the assessment of the risk of metastasis. *Cancer* 1986; **57** 160–71

7. Jahadi MR, Baldwin A. Villous adenomas of the colon and rectum. *Am J Surg* 1975; **130**: 729–32

8 Welch JP, Welch CE. Villous adenomas of the colorectum. *Am J Surg* 1976, **131**· 185–91

9 Kronborg O. Follow-up after removal of colorectal adenomas and radical surgery for colorectal carcinomas *Br J Surg* 1985, **72** Suppl : S26–8.

10. Chiu YS, Spencer RJ. Villous lesions of the colon *Dis Colon Rectum* 1978; **21**: 493–5.

11. Pheils MT Villous tumours of the rectum *Dis Colon Rectum* 1979; **22**· 406–7.

12. Hanley PH, Hines MO, Ray JE Villous tumours. experience with 217 patients. *Am Surg* 1971; **37**. 190–7

13 Miskowiak J, Lindenberg S Excision of rectal villous adenoma using TA or GIA stapler. *Br J Surg* 1986, **73**. 630.

14. Coller JA. Technical notes. Excision of villous adenoma of the rectum with a stapler. *Dis Colon Rectum* 1981, **24**: 407.

15. Kraske P Zur Exstirpation Hochsitzender Mast Darm Krebse. *Dtsch Vehr Ges Chir* 1885; **14**: 464. Quoted from Reference 17.

16 Mason AY Surgical access to the rectum: a trans-sphincteric exposure. *Proc R Soc Med* 1970, **63** Suppl : 91–4.

17 Wilson SE, Gordon HE Excision of rectal lesions by the Kraske approach. *Am J Surg* 1969; **118**: 213–17.

18. Soave F Hirschprung's disease· a new surgical technique. *Arch Dis Child* 1964, **39**: 116–24.

19 Parks AG, Stuart AE The management of villous tumours of the large bowel *Br J Surg* 1973, **60**. 688–95.

20. Thomson JPS. Treatment of sessile villous and tubulovillous adenomas of the rectum *Dis Colon Rectum* 1977, **20**: 467–72.

21. Morson BC Factors influencing the prognosis of early cancer of the rectum *Proc R Soc Med* 1966, **59**: 607–8.

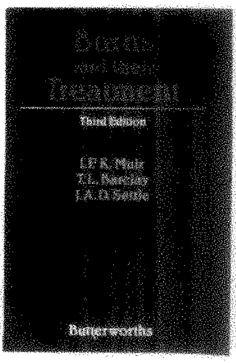
22 Biggers OR, Beart RW, Ilstrup DM. Local excision of rectal cancer. *Dis Colon Rectum* 1986; **29**: 374–7.

23. Grigg M, McDermott FT, Pihl EA, Hughes ESR Curative local excision in the treatment of carcinoma of the rectum *Dis Colon Rectum* 1984, **27**: 81–3.

Paper accepted 10 April 1988

BOOKS FROM BUTTERWORTHS

BURNS AND THEIR TREATMENT • Third Edition



I F K Muir MBE, VRD, MB, MS, FRCS, FRCS (Ed). Clinical Senior Lecturer in Surgery, University of Aberdeen, formerly Consultant in Plastic Surgery, Aberdeen General and Special Hospitals, UK.

T L Barclay MB, ChM, FRCS (Ed). Formerly Consultant Plastic Surgeon, Bradford Royal Infirmary and St. Luke's Hospital, Bradford; formerly Consultant Surgeon in Charge, Yorkshire Regional Burns Centre, Pinderfields Hospital, Wakefield, UK.

John A D Settle OBE, MPhil, MRCS, LRCP, DA. Consultant in Clinical Physiology, Director, Yorkshire Regional Burns Centre, Pinderfields General Hospital, Wakefield; Honorary Clinical Lecturer, Department of Surgery, University of Leeds, UK.

★ New edition of a classic work ★ Full colour section and numerous black and white illustrations ★ Authors have an international reputation ★ Up-to-date covering latest techniques in grafting; enlarged section on special site burns ★ Essential reading for plastic surgeons, accident and emergency personnel and nursing staff

"... here is the British Burns Bible, bang up to date and still at a very reasonable price. It is a must for all hospital libraries and all doctors and nurses faced with managing burns. There are good summaries at the ends of the chapters, and excellent references." *British Journal of Hospital Medicine*

Contents: Introduction · The scope of the burns problem · Treatment of burns shock · Local treatment of the burn wound · General care of patients with burns and scalds · Burns of special areas · Burns of special types · First aid and rescue out-patient treatment of major burns · Scars and contractures · Administrative aspects of burns · Index.

1987 196 pages 234 × 165mm Softcover Illustrated 0 407 00333 9 £25.00

Order this title from your usual bookseller or complete the coupon below.

ORDER FORM

To: **Butterworth & Co (Publishers) Ltd,**
Borough Green, Sevenoaks, Kent TN15 8PH, England
Telephone: (0732) 884567 Telex: 95678

24 Hour Order Line: (0732) 882566 – This line gives immediate access at any hour. Orders can be placed over the telephone by using your Butterworths account number or by charging to your credit account.

Cash or credit card details with order are essential except for account customers. Overseas orders not accompanied by a remittance will be charged postage and packing.

Please send me copy(ies) of **Burns and Their Treatment** at £25.00 0 407 00333 9

Please select preferred method of payment:

☐ I enclose remittance for £ ....

☐ Please debit my credit card as follows

☐ Access ☐ Barclaycard and other Visa cards
☐ American Express

Card Number

Expiry Date .... Signature ....

☐ Please include me on your mailing list

Name ....

Position ....

Address ....

Postcode ....

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. In the UK please allow 21 days for delivery.

Registered office: 88 Kingsway, London, WC2B 6AB Registered in England No 125354

For details of other Butterworth Scientific titles, please contact the appropriate office.
Orders should be sent to the appropriate office listed below.
The UK headquarters serves all UK and overseas markets except where there is a local Butterworths office.

United Kingdom
Butterworths, Borough Green
Sevenoaks, Kent TN15 8PH
England

Customers in Asia may order through:
Butterworth & Co (Asia) Pte Ltd
30 Robinson Road, Unit 12-01 Tuan Sing Towers
Singapore 0104, Republic of Singapore

USA & Canada
Butterworth Publishers
80 Montvale Avenue
Stoneham, MA 02180, USA

Australia & Papua New Guinea
Butterworths Pty Ltd, PO Box 345
North Ryde, New South Wales 2113
Australia

New Zealand
Butterworths of New Zealand Ltd
33-35 Cumberland Place
Wellington 1, New Zealand

BOOKS FROM BUTTERWORTHS

Rob and Smith's **Operative Surgery**

GYNAECOLOGY AND OBSTETRICS · Fourth Edition

Edited by **John M Monaghan** *FRCS(Ed), FRCOG Consultant Gynaecological Surgeon, Queen Elizabeth II Hospital, Gateshead, UK*

General Series Editors: **Hugh Dudley** *ChM, FRCS(Ed), FRACS, FRCS*
David C Carter *MD, FRCS(Ed), FRCS(Glas)*
R C G Russell *MS, FRCS*

* **Extensively revised and rewritten**
* **New international team of contributors**
* **Illustrations all redrawn by a single artist**

In order to reflect the best of modern practice the fourth edition of this volume in the Operative Surgery series has been completely rewritten and re-illustrated. The new editor has chosen a team of internationally recognised authorities to present their tried and tested approaches to the standard gynaecological operations. The implications of modern suture materials and surgical techniques such as the use of lasers and stapling guns are fully discussed. Also included are the newer diagnostic techniques which now demand the attention of the obstetrician and gynaecologist – chorion villus sampling and fetoscopy, for example. The presentations are complemented by detailed and clear drawings which provide step-by-step instruction to the application of the techniques.

The result is a broad and balanced coverage of all the important procedures which make up the daily practice of the gynaecological surgeon. Like its companions in the Series it will become the indispensable reference to surgical craft for all those in both training and practice.

Contents: Dilation and curettage • **Endometrial sampling and cytology techniques** • **Termination of pregnancy** • Suction • Middle trimester • Hysterotomy • **Operations on the vulva** • Simple vulvectomy • Bartholin's gland, removal and marsupialisation • Fenton's procedure • Urethral prolapse procedures • **Surgical treatment of CIN** • Electrocautery • Laser ablation • Cryosurgery • Cold coagulation • Cone biopsy, cold knife and laser • **Laparoscopy** • Diagnostic • Tubal occlusion • Second look • **Tubal ligation** • **Total abdominal hysterectomy** • **Vaginal hysterectomy** • **Operations for genital prolapse** • Anterior and posterior colporrhaphy • Manchester repair • Enterocoele repair • Le Fort procedure • **Operations for bladder dysfunction** • **Surgery of vesicovaginal and rectovaginal fistulae** • **Myomectomy** • **Operations for infertility** • Uteroplasty • Tuboplasty, micro and macrosurgical techniques • Ventrosuspension • **Surgery of endometriosis and pelvic infection** • **Surgery for benign ovarian disease** • **Surgery for malignant ovarian disease** • **Radical (Wertheims) hysterectomy** • **Radical vulvectomy and groin and pelvic node dissection** • **Radical vaginectomy** • **Exenterative surgery** • **Colostomy and urinary bypass procedures** • **Operations for the production of neovaginas** • Williams and McIndoes procedure • Gracilis myocutaneous transplants • Use of bowel transplants • **Laser surgery** • **Stapling techniques in obstetrics and gynaecology** • **Obstetric operations** • D & C evacuation of the uterus • Surgery of ectopic pregnancy • Surgery of recurrent abortion, including MacDonald and Shirodkar suture • Caesarean section • Surgery for the repair of obstetric trauma • Amniocentesis, fetoscopy and chorion villus sampling • Index

December 1987 320 pages 276 x 219 mm Hardcover Illustrated 0 407 00680 X £90.00

Order this title from your bookseller or in case of difficulty from the address below

For details of other Butterworth Scientific titles, please contact the appropriate office.
Orders should be sent to the appropriate office listed below.
The UK headquarters serves all UK and overseas markets except where there is a local Butterworths office.

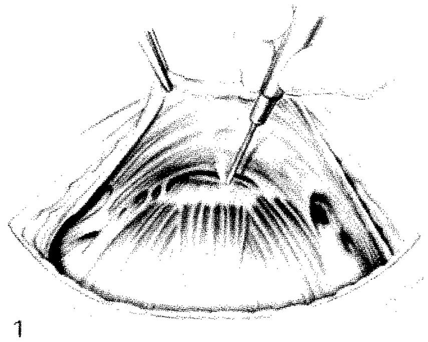
United Kingdom
Butterworths, Borough Green
Sevenoaks, Kent TN15 8PH
England

Customers in Asia may order through:
Butterworth & Co (Asia) Pte Ltd
30 Robinson Road, Unit 12-01 Tuan Sing Towers
Singapore 0104, Republic of Singapore

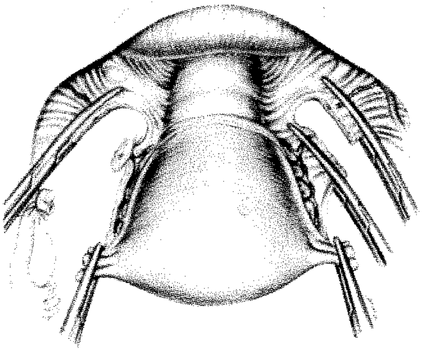
USA & Canada
Butterworth Publishers
80 Montvale Avenue
Stoneham, MA 02180, USA

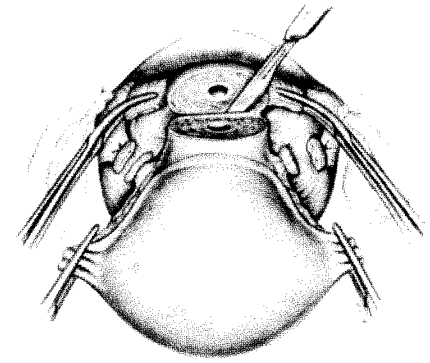
Australia & Papua New Guinea
Butterworths Pty Ltd, PO Box 345
North Ryde, New South Wales 2113
Australia

New Zealand
Butterworths of New Zealand Ltd
33-35 Cumberland Place
Wellington 1, New Zealand



1





Br. J. Surg. 1988, Vol. 75, September,
913–914

New technique of anastomosis after resection of left colon and rectum

V. I. Korepanov,
R. Sh. Chuntua and
S. P. Sugrobov

Hospital of Moscow Building Industry, Mitchurinsky Av. 56, 117192 Moscow, USSR

Correspondence to:
Dr V. I. Korepanov, Acad.
Millionshikov Str.,
35 Block 2 Apt 13,
115446 Moscow, USSR

A novel technique of 'autorecanalizing' anastomosis has been developed experimentally to reduce the risk of anastomotic failure when resection of the left colon or rectum is performed in the face of suboptimal bowel preparation. The method has been used in nine patients who presented with large bowel obstruction. One patient developed a low output faecal fistula that closed spontaneously within 19 days of operation. No leakage was detected in the remaining eight patients. The delay between operation and recanalization ranged from 8–13 days and the caecostomy used for intubation closed spontaneously within 24 days of surgery.

Keywords: Intestinal obstruction, caecostomy, intestinal anastomosis

Within the last 10–15 years new techniques have been elaborated to reduce the risk of anastomotic failure after resection of the left colon and rectum when bowel preparation has been poor. These techniques include whole-gut irrigation[1–4] and the recently described method of intra-operative wash-out introduced for emergency colon resection[5,6]. As a method of reducing the danger of anastomotic leakage, total/subtotal colon resection with ileorectal anastomosis has also been advocated in emergency surgery[7–9]. This paper describes a new technique which we have developed for anastomosis after resection of the colon and rectum.

Patients and methods

The type of anastomosis may be described as 'autorecanalizing'. After a midline laparotomy, the left colon and/or upper rectum is resected. Before mobilization, a stout ligature is placed around the colon at the intended site of proximal division of the bowel. At the distal resection line, the colon or rectum is transected below a crushing clamp leaving the distal segment open (*Figure 1*). The specimen is removed and both ends of the remaining bowel are approximated. The distal segment of the large intestine is sutured to the blind proximal segment with a single layer of interrupted inverting seromuscular sutures, the posterior walls being approximated first (*Figure 2*).

A long two-channel drainage tube of silicone rubber (outer diameter 10 mm) is then prepared by making 3–5 side holes in the distal end of the outer tube. The tube is then introduced into the lumen of the colon through a caecostomy or transverse colostomy (*Figure 3*). When performing a caecostomy a short rubber cuff can be used to adjoin the wall of the caecum to the anterior abdominal wall. The inner tube is used for irrigation, the outer for suction.

Autorecanalizing anastomoses have been performed in nine patients with obstructing cancer of the left colon or upper rectum. Starting in the immediate postoperative period, the drainage system is filled 3–5 times a day with 1500 ml saline under a pressure of 30–50 cmH$_2$O. After 5–15 min exposure to this pressure, the colonic contents are aspirated under a negative pressure of 30–50 cmH$_2$O. The drainage tube is withdrawn immediately after the first stool is passed per rectum. Contrast media can be infused through the tube to assess anastomotic healing before withdrawing the tube.

Results

Anastomotic leakage occurred in only one of the nine patients and was manifested by a moderate fever and wound suppuration. This was followed by the development of a low volume faecal fistula that closed spontaneously 19 days after surgery. The delay between operation and autorecanalization ranged from 8 to 13 days and the caecostomy closed spontaneously within 24 days of operation in all cases.

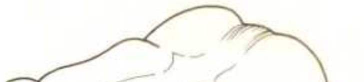


Figure 1 *The end of the proximal segment of colon is tied off forming a blind stump while the segment to be resected is closed by a crushing clamp before removal*

Discussion

Before using this technique in man, we have tested it in 36 mongrel dogs. Suture failure was not apparent in any animal at sacrifice and bursting pressure studies revealed a high resistance to pressure (>140 mmHg) over the first 4 days. Bursting pressure declined rapidly thereafter and autorecanalization was always achieved within 8–13 days of operation. Our clinical studies now suggest that the technique is safe and may have advantages over other methods described for use in patients with malignant large bowel obstruction.

Sykes[10] proposed a temporary transcutaneous colostomy that could be brought into operation on demand and 12 patients were operated upon without complications. Rickett *et al.*[11] described a balloon colostomy technique and presented data from 41 patients. The technique cannot be regarded as trouble-free in that five patients developed anastomotic dehiscence and three of them required a conventional colostomy. Prudkov and Uss[12] have modified the technique of defunctioning colostomy previously used by other Russian surgeons. In this method, the wall of the colon proximal to the anastomosis is sutured to the abdominal wall and opened in case of necessity. Of 47 patients

0007–1323/88/090913–02$3.00

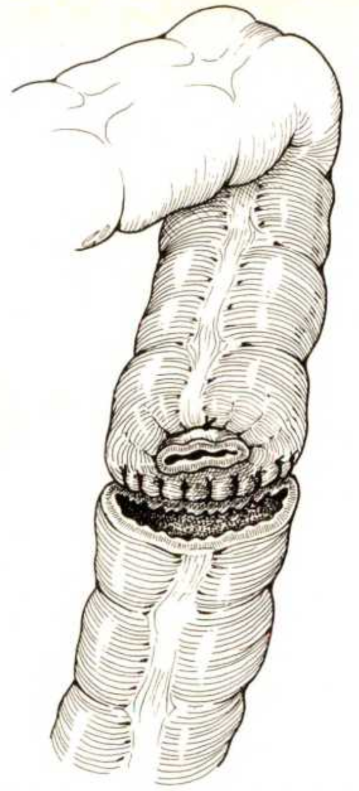


Figure 2 *The proximal segment is anastomosed to the distal one without opening the lumen of the proximal segment*

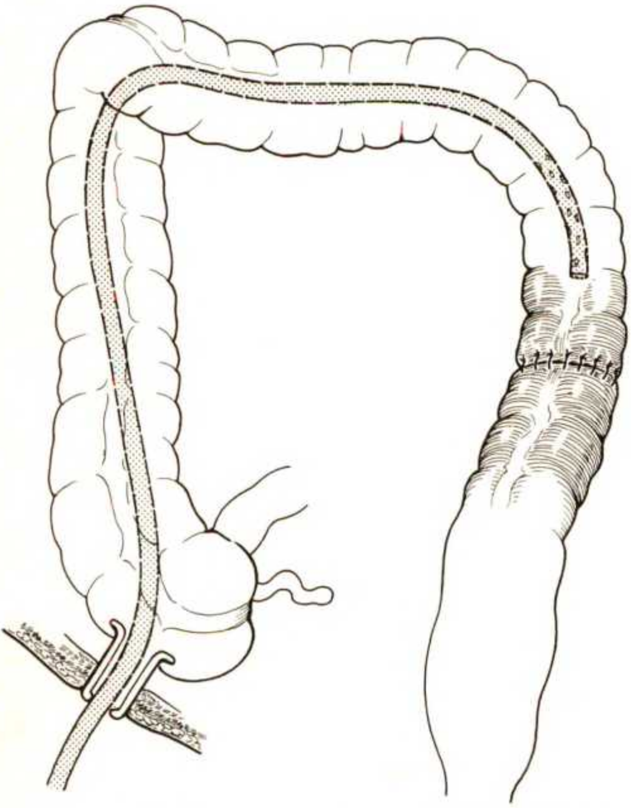


Figure 3 *The blind colonic segment is drained temporarily by a tube caecostomy as shown*

operated on the colostomy was brought into action in 9; all patients recovered and the colostomy closed spontaneously in every patient.

Ricklin[13] uses an 'end-to-side' rather than 'end-to-end' anastomosis in large bowel surgery and has reviewed a personal experience of 43 patients without anastomotic failure. He uses the end of the proximal segment as the colostomy so that it is sited a few centimetres distal to the end-to-side anastomosis. Unfortunately our experience demonstrated that the anastomosis not being challenged with intestinal content tends to become narrowed unless the stoma is closed as quickly as possible. Furthermore, this stoma can be closed only by a further operation. Sumin and Zhizhin[14] have elaborated a similar technique of 'end-to-side' intestinal anastomosis but use the distal segment of the gut as a stoma; this stoma usually closes spontaneously given time.

Despite their benefits, these techniques all have the disadvantage that gut decompression is passive rather than active. Our own technique is intended to be more active in that it entails alternate infusion of water into the gut and evacuation of the gut content. To prevent the suture line disrupting under the force of the infused solution we developed the technique of constructing a blind proximal colon segment. As shown experimentally, the resistance to bursting pressure within the blind stump is considerably higher than following a conventional anastomosis. In addition, the blind segment is well decompressed and therefore the anastomotic suture line is not exposed prematurely to high pressure.

All of our patients entered hospital with signs and symptoms of large bowel obstruction and could not have been prepared properly before semi-elective surgery. In the past they would have been dealt with by two-stage surgery using the Hartmann procedure. The new technique has allowed their successful management by a one-stage operation. Control endoscopic and X-ray examination undertaken up to 3 years after surgery has demonstrated that the diameter of the colon at the site of anastomosis is at least 2·5–3 cm and in some patients the anastomosis could not even be identified. None of the patients treated to date has presented with symptoms of bowel upset.

Acknowledgements

The illustrations were drawn by Gillian Oliver.

References

1. Hewitt J, Reeve J, Rigby J, Cox AG. Whole-gut irrigation in preparation for large bowel surgery. *Lancet* 1973; **ii**: 337–40.
2. Hollender LF, Calderoli H, Schoennahl C, Monteil H, Peteghem V, Meyer Ch. Notre experience de U irrigation lavage ('wash-out') dans la chirurgie colique. *Chirurgie* 1977; **103**: 769–79.
3. Huk I, Starlinger M, Schiessel R, Wewalka G, Rotter M. Orthograde Darmspulung zur praoperativen Darmvorbereitung. *Chirurg* 1980; **51**: 106–9.
4. Keighley MRB. A clinical and physiological evaluation of bowel preparation for elective colorectal surgery. *World J Surg* 1982; **6**: 464–70.
5. Dudley HAF, Radcliffe AG, McGeehan D. Intraoperative irrigation of the colon to permit primary anastomosis. *Br J Surg* 1980; **67**: 80–1.
6. Radcliffe AG, Dudley HAF. Intraoperative antegrade irrigation of the large intestine. *Surg Gynecol Obstet* 1983; **156**: 721–3.
7. Brief DK, Brener BJ, Goldenkranz R, Alpert J, Yalof I, Parsonnet V. An argument for increased use of subtotal colectomy in the management of carcinoma of the colon. *Am Surg* 1983; **49**: 66–72.
8. Morgan WP, Jenkins N, Lewis P, Aubrey DA. Management of obstructing carcinoma of the left colon by extended right hemicolectomy. *Am J Surg* 1985; **149**: 327–9.
9. Ryan JA, Oakley WC. Cecoproctostomy. *Am J Surg* 1985; **149**: 636–9.
10. Sykes FR. Transcutaneous defunctioning colostomy. *Br J Surg* 1979; **66**: 505–6.
11. Rickett JWS, Parivar F, Benfield JEC. Postoperative colonic decompression. *Ann R Coll Surg Engl* 1986; **68**: 211–3.
12. Prudkov ID, Uss GA. A modification of preventive colostomy and its use in resection of the large intestine. *Vestn Khir* 1981; **4**: 128–31.
13. Ricklin P. Zur Technik der Koloanastomosen. *Helv Chir Acta* 1982; **49**: 253–5.
14. Sumin VV, Zhizhin FS. Curative decompressive V-shaped stoma in resection of the intestine. *Vestn Khir* 1986; **12**: 81–6.

Paper accepted 11 April 1988

Br. J. Surg. 1988, Vol. 75, September, 915–916

Diagnosis and management of graft–enteric fistulae

H. W. Tilanus, O. T. Terpstra, P. de Smit, H. van Urk and H. F. Veen*

*Department of Surgery, University Hospital 'Dijkzigt', Erasmus University Hospital Rotterdam, The Netherlands, and * Surgical Department of the Ikazia Hospital Rotterdam, The Netherlands*

Correspondence to:
Dr H. W. Tilanus, Department of Surgery, University Hospital 'Dijkzigt', Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

During a 7-year period 20 patients underwent operation for a graft–enteric fistula after implantation of an intra-abdominal vascular prosthesis months or years before. Eighteen patients had gastrointestinal blood loss as their first symptom; 12 were in shock on admission. Fourteen patients had a fistula between the proximal anastomosis and the duodenum. Graft excision followed by axillobifemoral bypass was performed in 10 patients and four patients underwent local repair. A fistula between the distal anastomosis and the bowel was found in the remaining six patients and a local repair was carried out. Proximal graft–enteric fistula carries a particularly high postoperative mortality rate of more than 50 per cent.

Keywords: Aortic graft–enteric fistula, gastrointestinal bleeding, operation

The first case of graft–enteric fistula was reported by Brock[1] only 6 years after the first report of successful replacement of an aortic aneurysm[2]. Since then a constant flow of series and case reports in the literature have increased our knowledge of the diagnosis and management of this complication. The purpose of the present communication is to outline the management of these patients as we felt that in the earlier cases proper treatment was delayed even though the diagnosis was all too clear. Regardless of other possible causes of gastrointestinal bleeding, every patient with blood loss into the gastrointestinal tract after implantation of a vascular prosthesis needs a thorough work-up and eventually an exploratory laparotomy to rule out a graft–enteric fistula.

Patients and methods

Between 1 January 1978 and 1 August 1985, 20 patients were admitted to the University Hospital 'Dijkzigt' Rotterdam with symptoms of gastrointestinal blood loss after insertion of an abdominal aortic prosthesis contributing to a graft–enteric fistula. There was only one woman in the series The mean age was 66 years (range 55–77 years). The indication for the primary operation was a ruptured abdominal aneurysm in six patients, elective aneurysm surgery in another six patients and vascular occlusive disease in eight patients. The interval between the primary grafting and the first symptoms of gastrointestinal bleeding varied from 2 days to 15 years, with the majority of the patients developing bleeding symptoms between 2 and 5 years after operation.

Sixteen patients were anaemic and had gross intestinal bleeding with haematemesis, melaena or both. Twelve were in shock on admission. Seven patients had fever and four were septic on admission. Ultrasonography was performed in six patients. In only one patient was a false aneurysm seen. Seven patients underwent angiography; in two cases a false aneurysm was detected but lateral views were not obtained in the majority of cases. Gastroduodenoscopy was performed in 12 patients and revealed bleeding from the distal duodenum in 8 patients; in 4 of these 8 patients the bile-stained vascular prosthesis was visible in the duodenal erosion. Sixteen patients received broad spectrum antibiotics before operation (gentamicin and clindamycin or gentamicin and metronidazole with or without a cephalosporin).

At operation a fistula between the proximal anastomosis and the duodenum was demonstrated in 14 patients. Ten of these patients underwent graft excision and axillobifemoral bypass. In the other four patients a local repair, with closure of the suture line and bowel defect followed by interposition of an omental pedicle, was performed. Bacterial cultures from the graft–enteric fistula and surrounding contaminated area were performed in 14 patients. Nine of these cultures showed bacterial growth. The suture material used in the primary operation was Tevdek* 3-0 in six patients and Prolene* 3-0 in seven. In seven patients the suture material used was not recorded Of the 12 patients in shock on admission 6 died postoperatively. One of the four septic patients died and three of the four patients with local contamination only, without sepsis or shock, died during the postoperative period. Four of the nine patients with positive bacterial cultures died.

Of the ten patients undergoing graft excision, seven died in the postoperative period, three after aortic stump disruption and four from septic complications. Two patients died within 6 months of operation and only one patient is alive and well 1 year after operation. Of the four patients undergoing local repair, two died postoperatively, one owing to recurrent duodenal perforation and one after multiple organ failure. However, two are alive and well 1 and 2 years respectively after operation.

Six patients had a fistula between the distal anastomosis and the small bowel. In all of these six patients a local repair was performed, one patient died after operation but five are alive between 1 and 2 years after operation.

Discussion

The incidence of secondary aorto-enteric fistulae after aortic reconstruction has been estimated at between 0·4 and 2·4 per cent and in 75 per cent of cases the duodenum is involved[3–5]. This is explained by the intimate relation between the fourth part of the duodenum and the proximal anastomosis[6]. Such a close relationship between the bowel and the proximal or distal suture line may lead to pressure necrosis on the bowel wall giving rise to bowel perforation and prosthetic infection[7,8]. This is followed sooner or later by suture line haemorrhage with or without false aneurysm formation[9]. The interval between the initial operation and the development of a graft–enteric fistula can vary widely. There is often a period of minor gastrointestinal bleeding with or without intermittent sepsis for weeks or months which heralds the major bleed[10,11].

This period which foreshadows major symptoms is most important because the two key points in a favourable outcome are early diagnosis and early surgical intervention. The low yield of various diagnostic studies is well documented[12,13] and confirmed by our study. Even gastroduodenoscopy, in our view the most important diagnostic test, detected the graft–enteric fistula in only 8 of the 12 patients endoscoped. However, endoscopy is also an important tool with which to rule out more common causes of haemorrhage Arteriography should be performed only when the patient's condition is stable. Extravasation of contrast into the bowel confirms the diagnosis[5]. Lateral views are mandatory in order to rule out a false aneurysm, especially at the proximal anastomosis[14] Of the seven angiograms in our series a false aneurysm was seen in only two patients. Extravasation into the bowel was never observed. If a graft–enteric fistula cannot be ruled out by imaging techniques or endoscopy, laparotomy should be performed before major bleeding occurs. The operative management of a graft–enteric fistula is a matter of controversy. Successful retention of the old graft with local repair by direct suture and interposition of an omental pedicle between bowel and graft has been reported[15,16]. In the event of a fistula between the duodenum and the proximal anastomosis the outcome after local repair was slightly better than after total graft excision. However, there remains the possibility of retroperitoneal sepsis, spreading graft infection and recurrent fistula formation. Some authors advocate total graft excision and extra-anatomic reconstruction in the treatment of proximal fistulae[17].

---

* *Prolene is a registered trademark of Ethicon Ltd., UK, Tevdek is a registered trademark and is manufactured by Tecnatel*

Others have reported successful placement of a new graft in the same location after excision of the infected graft[18] but the approach may have to be modified in the face of more complicated graft infection. Further definition is needed to differentiate those patients requiring total graft excision from those that are best treated by local repair. Between these two extremes there may indeed be a place for graft excision and insertion of a new graft in the same location possibly in patients with proximal fistulae without extensive graft infection. In patients with a graft–enteric fistula without extensive graft infection we are currently inclined to choose local repair, especially in those with distal fistulae. On the other hand, when the fistula is secondary to or coupled with spreading graft infection, excision with closure of the aortic stump and extra-anatomic bypass is now performed. In this small series no definite conclusions can be drawn regarding the influence of the hypotensive state, septic situation or degree of contamination in relation to morbidity and mortality. However, we have the impression that the more widespread the graft infection, the greater the mortality regardless of the clinical situation on admission.

Prevention of this disastrous complication remains the primary goal. This can be accomplished by a number of measures. The technical perfection of the anastomosis and prevention of a false aneurysm or a haematoma around the prosthesis have been recognized as being of utmost importance[19]. Regarding the proximal anastomosis, the fourth part of the duodenum should be mobilized as a free intraperitoneal organ, thus avoiding pulling of the duodenum against the constant pulsation of the graft-aortic suture line[20].

Complete coverage of the prosthesis with an omental flap to prevent a close relationship between the bowel and the vascular graft is advocated by many authors[21–23]. When difficulty is encountered in coverage it is relatively simple to pass an omental flap through a window in the transverse mesocolon[24]. Prevention of graft infection is another important factor. Contamination may be from the environment or from unrecognized enteric injury at time of operation. The importance of antibiotic prophylaxis in vascular surgery has been widely recognized[25–26]. Graft–enteric fistula is a complication that can be easily prevented but which, once present, is life threatening. Gastrointestinal blood loss after aortic surgery is a signal for an aggressive attempt at early diagnosis and early treatment is mandatory.

Acknowledgements

The authors are very grateful to Mrs Leny Hopman-Andressen and Miss Ariane van Bommel for preparing and revising the manuscript.

References

1. Brock RC. Aortic homografting: a report of six successful cases. *Guy's Hosp Rep* 1953; **102**: 204–28.
2. Dubost C, Allary M, Oesonomos N. Resection of an aneurysm of the abdominal aorta· reestablishment of continuity by a preserved human arterial graft with result after five months. *Arch Surg* 1952; **64**: 405–8
3 Elliot JP, Smith RF, Szilagyi DE. Aorto-enteric and paraprosthetic-enteric fistulas. *Arch Surg* 1974; **108**. 479–90.
4 Kleinman LH, Towne JB, Bernhard UM. A diagnostic and therapeutic approach to aorto-enteric fistulas: clinical experience with twenty patients *Surgery* 1979; **86**. 868–80.
5. Thompson WH, Jackson DS, Johnsrude JS. Aorto-enteric and paraprosthetic-enteric fistulas: radiologic findings *AJR* 1976; **127**: 235–42.
6. Shucksmith HS. Duodenal, sigmoid and ureteric fistulas resulting from aorta-iliac grafts or endarterectomy. *Br J Surg* 1968; **116**: 460–2.
7 Dietrick EB, Noon GP, Liddicoat JE, DeBakey ME. Treatment of infected aorto-femoral arterial prosthesis *Surgery* 1970; **68**: 1044–52.
8. Najafi H, Javid H, Dye WS, Hunter JA, Julian OC Management of infected arterial implants. *Surgery* 1969, **65**: 539–47
9. Doss T. Small bowel erosion after aortic replacement by synthetic graft. *Am J Surg* 1968; **116**· 460–2
10. Lise M, Yacoub MH. Aorto duodenal fistula. a complication of abdominal aortic grafts. *J Cardiovasc Surg* 1969; **10**. 172–7.
11. Rosato FE, Barker C, Roberts B. Aorto intestinal fistula. *J Thorac Cardiovasc Surg* 1967, **53**: 511–4.
12. Kierhan PD, Pairolero PC, Hubert JP Jr, Mucha P Jr, Wallace RB. Aortic graft enteric fistula *Mayo Clinic Proc* 1980; **55**. 731–8.
13. Rosenthal D, Deterling RA Jr, O'Donnel TF, Callow AD. Positive blood culture as an aid in the diagnosis of secondary aorto enteric fistula. *Arch Surg* 1979; **114**: 1041–4.
14 Schuette HE. Angiographic signs of aortic graft-enteric fistulas. *Clin Radiol* 1987; **38**. 503–8.
15. Brenner WI, Richman H, Reed GE. Roof patch repair of an aortoduodenal fistula resulting from sutureline failure in an aortic prosthesis *Am J Surg* 1974, **127**: 762–4.
16. Ray FS, McAfee RE, Hiebert CA, Hall WJ Aortoduodenal fistula· primary repair with saphenous vein patch graft. *JAMA* 1976; **236**: 2423–7.
17. Umpleby HC, Britton DC, Turnbull AR. Secondary aorto enteric fistula: a surgical challenge. *Br J Surg* 1987; **74**· 256–9.
18. Walker WE, Cooley DA, Duncan JH, Hallman GL Jr, Ott DA, Reul CJ. The management of aortoduodenal fistula by in situ replacement of the infected abdominal aortic graft. *Ann Surg* 1987, **205**: 727–32.
19 Buchbinder D, Leather R, Shah D, Karmody A Pathologic interactions between prosthetic aortic grafts and the gastrointestinal tract. *Am J Surg* 1980; **140**: 192–8.
20 Miller D. Prevention of aortoduodenal fistula by duodenal reflexion. *Am J Surg* 1979, **138**· 332–3.
21. O'Mara CS, Williams GM, Ernst CB. Secondary aorto enteric fistula. *Am J Surg* 1981; **142**: 203–8.
22. Connelly JE, Kwaan JHM, McCant PM. Aortoenteric fistula. *Ann Surg* 1981; **194**. 402–12.
23. Levy MJ, Todd DB, Lillehei CW, Varco RL Aortointestinal fistulas following surgery of the aorta. *Surg Gynecol Obstet* 1965; **120**· 992–6
24. Iliopoulos JJ, Pierce GE, Thomas JH, Hermreck AS. Transmesocolic omentoplasty. *Surg Gynecol Obstet* 1983; **157**: 283–4
25 Bunt TJ. Synthetic vascular graft infections. *Surgery* 1983; **96**. 773–46.
26 Busuttil RW, Rees W, Baker JD, Wilson SE. Pathogenesis of aortoduodenal fistula *Surgery* 1979, **85**: 1–13

Paper accepted 12 April 1988

Br. J. Surg. 1988, Vol. 75, September, 917

Rectus nerve entrapment causing abdominal pain

P. N. Hall and A. P. B. Lee

West Suffolk Hospital, Hardwick Lane, Bury St. Edmunds, Suffolk, UK
Correspondence to: Dr P. N. Hall, Dudley Road Hospital, Dudley Road, Birmingham B18 7QH, UK

Gray and Collin[1] have recently reviewed non-specific abdominal pain as a cause of acute admissions to hospital. They mention rectus nerve entrapment syndrome which we, like Doouss and Boas[2], believe is commonly missed since the abdominal wall is not thought about when examining patients.

Patients and methods

Twenty-four patients in 2 years were referred to the pain clinic. All had been investigated by either surgeons or gynaecologists, who had excluded intra-abdominal pathology. Fourteen had had previous surgery for proven organic disease (*Table 1*). None had had negative laparotomies for their pain. Twenty-one patients were female. The group represents approximately 15 per cent of patients referred with non-specific abdominal pain

Table 1 *Patients referred to the pain clinic and found to have rectus nerve entrapment*

		Total
Idiopathic group	2 Male	
	8 Female	10
Patients with previous surgery		
Pfannenstiel incision	6 Female	
Appendicectomy	4 Female	
Midline incision (nylon mass closure)	2 Female	
Herniotomy	1 Female	
Lumbar sympathectomy	1 Male	14

Results

Diagnosis of rectus nerve entrapment

All patients had one or occasionally two trigger points localized with one finger with repeated accuracy. Always the surface marking was just medial to the linea semi-lunaris of the rectus sheath Tensing the recti always made the pain worse and usually enabled one to palpate a dimple at the site of the trigger point. Needling deeply into this area reproduced the pain or elicited paraesthesia and a transient cure was produced on infiltration with 0·25 per cent bupivacaine.

In those with surgical scars the trigger points were always 3 cm or further from them and were not, in our opinion, due directly to the closure material. The timing of surgery to presentation of pain ranged from 1 to 25 years.

In the non-surgical group only two out of ten cases could associate their pain with recent muscular strain. The remaining eight cases appear idiopathic.

Treatment

The method of treatment and the results obtained in patients are set out in *Table 2*. Three have had surgical decompression of the tunnels and three to date remain uncured.

Table 2 *Results of treatment*

Treatment	Cured
Bupivacaine test	2
Repeated bupivacaine	2
Bupivacaine with 40 mg Depo-Medrone® (methylprednisolone acetate)	7
6 per cent aqueous phenol	2
Radiofrequency lesions	5
Surgical decompression	3
Persistent symptoms	3

Each patient started with the bupivacaine test and progressed down the treatment schedule until cured. Depo-Medrone is a trademark of Upjohn Ltd, Crawley, UK

Discussion

For those aware of rectus nerve entrapment syndrome, the diagnosis is easy. Applegate[3] has described how the neurovascular bundle containing the anterior branches of the intercostal nerves turn rather sharply at the lateral border of the recti in order to run through fibrous tunnels in the muscle. He suggests that the trigger point is produced by herniation of the bundle with its protective fat pad through wide gaps in the anterior rectus sheath. These gaps, we feel, correspond to the dimple we find clinically.

The strikingly accurate localization of pain by all the patients to the correct anatomical surface marking for these tunnels makes us believe the symptoms to be genuine. Like Mehta and Ranger[4] we did not feel that placebo treatment was justified. Of 24 cases, 14 had their trigger points at McBurney's point or its left-sided equivalent. Perhaps the absence of a posterior sheath at this level, allowing greater excursion of the muscles, is more likely to provoke an entrapment. Kamar and Varga[5] have shown disturbed electromyograms in such patients.

The observations of Travell and Rinzler[6] and Good[7], that the effects of local anaesthetics can be considerably longer than their expected duration of action, is confirmed. Some obtained relief for weeks, and two patients were cured. Travell and Rinzler[6] suggest that this is due to breaking of the reflex pain cycle. Treatment with 5 per cent aqueous phenol by Mehta and Ranger[4] and local anaesthetics with depot steroids by Tung[8] *et al.* appear more successful than in these patients. In conclusion, the clinician should be aware of the possibility of rectus nerve entrapment when examining a patient with abdominal pain. The diagnosis is simple but, in some, the treatment is difficult.

References

1 Gray DWR, Collin J Non-specific abdominal pain as a cause of acute admission to hospital *Br J Surg* 1987; **74** 239–42
2. Doouss TW, Boas RA The abdominal cutaneous nerve entrapment syndrome. *NZ Med J* 1975, **81** 473–5
3. Applegate WV. Abdominal cutaneous nerve entrapment syndrome. *Surgery* 1972, **71** 118–24
4 Mehta M, Ranger I. Persistent abdominal pain Treatment by nerve block. *Anaesthesia* 1971; **26** 330–3
5. Kamar J, Varga B Syndrome of rectus abdominis muscle *J Neurol* 1975; **201** 121–5
6. Travell J, Rinzler SN. The myofascial genesis of pain *Postgrad Med* 1952; **11** 425–34
7. Good MG. Pseudo-appendicitis *Acta Med Scand* 1950, **138** 348–53
8 Tung AS, Tenicela R, Gioranetti J Rectus abdominis nerve entrapment syndrome *JAMA* 1978, **240** 738–9

Paper accepted 1 November 1987

0007–1323/88/090917–01$3 00

Br. J. Surg. 1988, Vol. 75, September, 918–919

Wound infection after breast biopsy

J. M. Dixon, U. Chetty and A. P. M. Forrest

University Department of Surgery, Longmore Breast Unit, Edinburgh, UK

Correspondence to: Mr J. M Dixon, University
Department of Surgery, Royal Infirmary,
Edinburgh EH3 9YW, UK

Breast biopsy is a 'clean' operation normally associated with a low incidence of wound infection. We have presented evidence that the lesions of periductal mastitis/duct ectasia[1] are not sterile[2,3] and, if this is so, breast biopsy for this condition should be associated with an increased frequency of wound infection. In this study we have compared wound infection rates in more than 300 patients undergoing breast biopsy with the histology of the excised specimen.

Patients and methods

The study was performed on 338 patients having a breast biopsy, 148 under general and 190 under local anaesthesia. Most were included in a controlled trial of adrenaline in breast surgery[4]. All wounds were examined 8–13 days after operation by the same group of surgical staff and wound complications were noted. Patients with wound problems were reviewed at weekly intervals until these resolved. A wound infection was recorded only if there was a discharge of pus from the wound in the postoperative period.

Bacteriology

Dry swabs from all but one infected wound were submitted to the laboratory and cultured on blood agar (Columbia agar base CM331, Oxoid Ltd., Basingstoke, UK) and MacConkey agar (CM109, Oxoid Ltd.) and incubated aerobically in 10 per cent oxygen. Blood agar plates were also incubated anaerobically in 10 per cent carbon dioxide. Identification of organisms was by routine laboratory methods.

Pathology

The histology of the excised specimen was that reported by routine examination, except for the biopsies diagnosed as periductal mastitis or duct ectasia. These were reviewed and if the diagnosis was confirmed the degree of periductal inflammation and duct dilatation was graded as previously described[1].

> Periductal inflammation I, acute inflammation or severe chronic inflammation with granuloma formation, II, moderate chronic inflammation, III, minor chronic inflammation.
>
> Duct dilatation. I, no ducts dilated; II, occasional ducts dilated, III, many ducts dilated.

All patients with histologically proven periductal mastitis/duct ectasia presented with either breast pain, a mass with or without overlying skin inflammation, nipple discharge or nipple retraction. Comparison of the frequency of wound infection in different groups was performed by either the χ^2 or Wilcoxon rank sum tests

Results

There were 14 wound infections in the 338 patients, an incidence of 4 per cent. A comparison of the frequency of wound infection and the histopathological diagnosis is given in *Table 1*. Nine wound infections occurred in the eighty-eight (10·2 per cent) patients with a histological diagnosis of periductal mastitis/duct ectasia compared with 5 in the 250 (2·0 per cent) patients with other pathologies. This difference was highly significant ($P < 0{\cdot}001$).

The organisms isolated are shown in *Table 1*. Enterococci and *Bacteroides* sp. were seen only in the periductal mastitis/duct ectasia group.

The use of adrenaline did not appear to influence wound infection rates (*Table 2*). Wound haematomas and bruising were also unrelated to the use of adrenaline[1]. Infection developed in 2 of the 15 wounds with (13 per cent) and 12 of 323 wounds without (3·7 per cent) haematomas. This difference was not significant and did not account for the difference in infection rates.

Patients with periductal mastitis/duct ectasia

The rates of wound infection in patients with varying degrees of periductal inflammation and duct dilatation are shown in *Table 3*. There appeared to be a direct correlation between the frequency of wound infection and the histological features of active inflammation and non-dilated ducts. Because of the small numbers in each group the differences reached statistical significance only when the group with either acute/severe chronic periductal mastitis or no dilated ducts were compared with the other two groups combined

The relationship between clinical features and wound infection is presented in *Table 4*. Patients presenting with inflammatory masses were most likely to develop postoperative infection.

Table 1 *Comparison of the frequency and bacteriology of wound infections with the histopathology in patients undergoing breast biopsy*

Histological diagnosis	Number of patients	Number with infection	%	Organisms isolated
Carcinoma	17	1	2·0	*Staphylococcus aureus*
Benign mammary dysplasia	133	2		*Staphylococcus albus* No growth
Fibro-adenoma	48	1		Not sent
Other benign*	52	1		No growth
Periductal mastitis/ duct ectasia	88	9	10·2	No growth ×2 *Staphylococcus albus* *Staphylococcus aureus* Enterococci ×2 *Bacteroides* ×3

* Other benign includes normal breast, papillomas, sclerosing lesions and fat necrosis

Table 2 *Influence of adrenaline on wound infection rate in patients whose breast biopsies showed evidence of periductal mastitis/duct ectasia or other pathologies*

Pathology	Adrenaline	Number of patients	Number with infection	%
Other	No	132	3	2·3
Other	Yes	118	2	1·7
PDM/DE	No	46	5	10·9
PDM/DE	Yes	42	4	9·5

PDM, periductal mastitis; DE, duct ectasia No significant differences were found between groups

Table 3 *Pathological features of patients with periductal mastitis/duct ectasia related to frequency of wound infection*

Pathological features	Number of patients	Number with infection	%
Inflammation			
Acute/severe chronic	24	5	21
Moderate chronic	38	3	8
Minor chronic	26	1	4
Ducts dilated			
None	22	5	23
Occasional	35	3	9
Many	31	1	3

There was no significant direct correlation between histological factors and the frequency of wound infection A significantly greater rate of wound infection was found in groups with acute inflammation and no dilated ducts when compared with the other two groups combined ($P<0.05$ in both cases)

Table 4 *Presenting symptoms of patients with periductal mastitis/duct ectasia related to the frequency of wound infection*

Symptoms	Number of patients	Number with infection	%
Pain	18	2	11
Mass no inflammation	20	1	5
Mass + inflammation	6	4	67
Nipple discharge	24	2	8
Nipple retraction	20	0	0

There was a significantly greater infection rate in patients with mass + inflammation, $P<0.0001$

Outcome of infections

By 3 weeks the wounds of four of the five patients with other pathologies and four of the nine with periductal mastitis had healed. One patient, with a wound infection after a biopsy for cancer, healed at 4 weeks following a course of flucloxacillin. Two of the five patients with periductal mastitis whose wounds had not healed by 3 weeks were treated with metronidazole alone and one received metronidazole and cephradine. These three wounds had healed by 6 weeks. Three wounds did not heal due to the development of a mammillary fistula. Two of these patients were in the group of six who had presented with a periareolar inflammatory mass.

Discussion

This study indicates that wound infection after surgery for periductal mastitis/duct ectasia is more common than for other benign or malignant conditions of the breast. Although the numbers are small, it also suggests that the bacteria associated with this increase in infection rate are enterococci and *Bacteroides*, the same organisms which we have previously noted to be present in the nipple discharge of patients with periductal mastitis/duct ectasia[2,3]. Further evidence for the relationship of these organisms to this condition comes from reports that the same bacteria can be isolated from non-lactating breast abscesses[5,6] which occur as a complication of periductal mastitis/duct ectasia[2,3].

We believe that periductal mastitis is part of the syndrome which includes duct ectasia, non-lactating breast abscesses and mammillary fistulae[7]. The finding that wound infections are more frequent in patients with acute or active chronic inflammation and no duct dilatation suggests that bacteria may be the cause of this initial inflammation. Resolution of periareolar inflammation with a combination of metronidazole and flucloxacillin[2] supports this suggestion. Thus the theory that the lesions of periductal mastitis/duct ectasia become infected as a result of stasis of secretions may be incorrect.

In view of these findings, the value of perioperative antibiotics in certain patients with periductal mastitis/duct ectasia needs to be investigated.

Acknowledgements

We are grateful to our colleagues who reported the histopathology of the specimens in the study through the routine pathological service; and also to our colleagues in the department of microbiology who reported the bacteriology of the wound infections. Thanks are also accorded to Dr R.A. Elton for statistical assistance and to the nursing staff of Longmore Hospital for their care of these patients.

References

1. Dixon JM, Anderson TJ, Lumsden AB, Elton RA, Roberts MM, Forrest APM. Mammary duct ectasia. *Br J Surg* 1983; **70**: 601–3.
2. Dixon JM, Bundred NJ Mammary duct ectasia—studies of factors involved in its aetiology and pathogenesis *Breast News* 1986, 4: 1–5.
3. Bundred NJ, Dixon JM, Lumsden AB, Chetty U, Forrest APM. Are lesions of duct ectasia sterile? *Br J Surg* 1985; **72** 844–5
4. Dixon JM, Crofts TJ, Armstrong CP, Lee D, Wilson J, Forrest APM. The advantage of adrenaline in local and general anaesthetic breast biopsy *J R Coll Surg Edinb* 1983, **28**: 292–4.
5. Pearson NE. Bacteroides in areolar breast abscesses. *Surg Gynecol Obstet* 1967; **125**: 800–2.
6. Leach RD, Eykyn S, Phillips I, Corrin B. Anaerobic subareolar breast abscesses. *Lancet* 1979; **i**: 35–7
7. Bundred NJ, Dixon JM, Chetty U, Forrest, APM. Mammillary fistula. *Br J Surg* 1987; **74**: 466–7

Paper accepted 6 December 1987

Br. J. Surg. 1988, Vol. 75, September, 920–921

Misdiagnosis of breast cancer in an out-patient breast clinic

E. Siim, J. Kjærgaard, F. Rank*, H. Baden and B. Lundbæk†

*Department of Surgical Gastroenterology D, *Institute of Pathology and †Department of Radiology, Herlev Hospital, University of Copenhagen, Denmark*

Correspondence to: Dr E Siim, Kirsten Piils Vej 10,
DK 2920 Charlottenlund, Denmark

The value of the several diagnostic modalities in breast cancer is well known, but the incidence of missed cancers in women referred with breast complaints is not well recorded. We present our experience to establish a yardstick for the efficiency of diagnostic programmes and to discuss the failures.

Methods

During 1978, 308 women were referred by general practitioners to the Breast Clinic at Herlev Hospital for a wide range of breast complaints. Of these referrals, 83 had breast cancer and 225 were discharged with a benign diagnosis, in 124 cases based on a biopsy.

The women were submitted to a diagnostic programme[1], based on three main principles diagnosis and treatment are carried out as far as possible in the out-patient department, diagnosis should be quickly established and with as few visits as possible, and a diagnosis of cancer is made before admission for mastectomy

In the out-patient department physical examination was performed by a senior resident or consultant. Mammography was performed in all patients and ductography when indicated. Cysts were needle-aspirated, small solid lumps were removed and knife biopsies taken from larger, less-defined lesions. Subclinical clusters of microcalcifications found on mammography were removed surgically after marking with a hook-wire[2].

At the follow-up investigation in 1982 the same diagnostic procedures were used.

Follow-up investigation

Four years later the 225 women with a former diagnosis of benign breast disease received a questionnaire and were offered a clinical examination and mammography. In all, 190 women returned the questionnaire, among these 170 consented to palpation and mammography in the Breast Clinic A search was made for 35 non-responders in the Danish Cancer Registry to find out if any of these 35 women had developed breast cancer during the 4-year observation period (1978–1982). All 124 former breast biopsies from 1978 were re-evaluated by an expert in breast pathology with no knowledge of the original histological diagnosis. The mammograms were re-evaluated.

Results

Among the 225 women, 6 had developed breast cancer and 1 patient had developed carcinoma *in situ* (*Table 1*). The observation period (1978–1982) ranged from 16 to 55 months, as 1 patient (No. 7) 16 months after her first visit had already complained about breast symptoms and breast cancer was diagnosed. Four other patients (Nos. 1, 4, 5 and 6) during this 4-year observation period had presented with symptoms such as pain, tenderness or a lump. Examination, mammography and biopsy revealed cancer and a mastectomy had been performed. The last two patients had breast cancer diagnosed at the follow-up investigation. Patient No. 2 presented an obvious malignant tumour and patient No. 3 had suspicious microcalcifications on mammography which proved to be carcinoma *in situ* on biopsy. In patients Nos. 5 and 6 the cancer occurred in the contralateral breast.

In patient No. 7 the physical findings in 1978 had been equivocal as to whether a lump could be palpated or not. No biopsy had been taken and the patient had been discharged without further appointments. The mammogram at this time did not indicate cancer. The cancer was diagnosed 16 months later at the site that had originally been under suspicion.

In four patients (Nos. 1–4) the cancer also occurred in the area where the original biopsies had been taken in 1978. The pathology report then was fibrocystic disease. Re-evaluation in 1982 changed the diagnosis to atypical ductal hyperplasia in three cases and ductal carcinoma *in situ* in one case. This last patient had had a contralateral mastectomy owing to ductal carcinoma in 1973.

The re-evaluation of all the 124 slides from 1978 showed that 4 of those previously diagnosed as fibrocystic disease had the diagnosis changed to atypical hyperplasia and 4 of those diagnosed as atypical hyperplasia were re-classified as fibrocystic disease, while one turned out to be carcinoma *in situ* (*Table 2*).

During the follow-up investigation 12 patients had a breast biopsy performed, the biopsies were taken from the same breast as in 1978. In six patients the diagnosis was unchanged, but in five fibrocystic disease had changed into atypical ductal hyperplasia, and in one atypical hyperplasia had changed to carcinoma *in situ*.

Re-evaluation of all 225 mammograms from 1978 confirmed the initial diagnosis.

Table 1 *The seven patients developing breast cancer*

Patient no.	Age at mastectomy	Re-examined 1978 histological slides	Observation period	Tumour size	Cancer in same breast as in 1978 symptoms	Histological diagnosis of mastectomy specimen
1	46 years	Ductal papillomatosis and atypical hyperplasia	47 months	1 cm	Yes	Mammary carcinoma, ductal type
2	59 years	Atypical hyperplasia	55 months	5 cm	Yes	Mammary carcinoma, mucinous type
3	53 years	Atypical hyperplasia	49 months	3 cm	Yes	Carcinoma *in situ*, ductal type
4	54 years	Carcinoma *in situ*, ductal type, multiple	21 months	0 5 cm 0 7 cm 1 cm	Yes	Mammary carcinoma, ductal type, multiple
5	58 years	No biopsy	47 months	2 cm	No	Mammary carcinoma, lobular and ductal type, multiple
6	54 years	No biopsy	34 months	1 cm	No	Mammary carcinoma, ductal type
7	65 years	No biopsy	16 months	2 cm	Yes	Mammary carcinoma, ductal type

Table 2 *Re-evaluation of tissue slides from biopsies in 1978*

		Re-evaluated diagnosis		
Diagnosis	1978	Atypical hyperplasia	Carcinoma *in situ*	Fibrocystic disease
Fibrocystic disease	118	4	—	114
Atypical hyperplasia	6	1	1	4
Total	124	5	1	118

Discussion

Cancer of the breast is the most frequent malignant disease in women. The incidence in Denmark is approximately 83/100 000 per year[3].

The apparent incidence in our material is almost 0.8 per cent, approximately a tenfold greater incidence than in the background population. According to life table analysis there is a significant difference in the two cancer rates. This is disappointing because 4 years earlier the 225 women had been screened and declared free of malignancy.

However, revision of the slides from the seven patients who later developed cancer or carcinoma *in situ* revealed that one patient already had carcinoma *in situ*, while three patients had atypical ductal hyperplasia (*Table 1*). Atypical ductal hyperplasia is a pre-cancerous condition which demands repeated examination because of its known cancer risk[4–6]. Microscopically, there are pre-malignant changes both in cell pattern and cytology[7,8].

One patient was clinically misdiagnosed in 1978. She had a lump, but no biopsy was taken. Sixteen months later malignancy was detected in the same lump.

Among the seven patients with breast cancer and carcinoma *in situ*, four were thus histologically misdiagnosed in 1978, one was a clinical error.

The last two patients developed cancer in the contralateral breast during the observation period. The conclusion to be drawn from this study is that careful and experienced histological assessment is required, and patients with atypical ductal hyperplasia do progress to carcinoma.

References

1. Kjaergaard J, Christensen U, Blichert-Toft M, Baden H. Diagnosis of diseases of the breast in out-patients clinic. *Ugeskr Læger* 1982; **144**. 232–4.
2. Frank HA, Hall FM, Steer ML. Preoperative localization of nonpalpable breast lesions. Demonstrated by mammography. *N Engl J Med* 1976; **295**. 254–60
3. Ewertz M, Møller-Jensen O. Mammary carcinoma in Denmark 1943–1976. *Ugeskr Læger* 1981; **143**. 2758–60
4. Brooks P. Epidemiology and risk factors in breast cancer. *J Reprod Med* 1982; **27**. 670–4
5. Kelsey HL, Hildreth NG, Thompson WD. Epidemiological aspects of breast cancer. *Radiol Clin NA* 1983; **21**: 3–12
6. Lance LL. Risk factors for benign breast disease. *Am J Epidemiol* 1981; **114**. 606–7
7. World Health Organization. *Histological typing of breast tumours* 2nd ed. Geneva 1981.
8. Azzopardi JG. *Problems in Breast Pathology*. London: Saunders, 1979: 92–112, 167–239.

Paper accepted 10 February 1988

Br. J. Surg. 1988, Vol. 75, September, 921–922

Ultrasound scanning by the urologist in outpatient clinics

S. G. Vesey, P. J. O'Boyle and G. N. Lumb

Department of Urology, Musgrove Park Hospital, Taunton, Somerset TA1 5DA, UK

Correspondence to Mr P. J. O'Boyle

Abdominal ultrasound plays an important role in the diagnosis of genito-urinary tract pathology and has largely replaced intravenous urography as the initial investigation of choice[1]. Ultrasonography can normally be conducted without special preparation of patients; it is quick, non-invasive and radiation-free. This flexibility makes diagnostic ultrasound an ideal investigation for use in the outpatient department[2], while the information obtained regarding bladder volume, hydronephrosis and prostate size is comparable to that of formal radiological investigation[3,4].

However, it is frequently not practical for the radiology department to provide an immediate ultrasound service during a urology outpatient clinic. Instead, patients referred for ultrasonography are asked to return for a further appointment convenient to the work schedule of the department. Ideally, this should coincide with the next urology clinic appointment, but in practice the patient may well require three visits before a definitive clinical decision is taken based on the ultrasound report. This is inefficient for both patient and doctor and in economic terms is wasteful of hospital resources.

It was decided, therefore, to evaluate the efficiency and cost-effectiveness of providing an immediate ultrasound service in the urological outpatient department. The scans were performed by the urologist himself after a short period of basic training in ultrasonography.

Patients, methods and results

A total of 679 patients, 532 (78 per cent) men and 147 (22 per cent) women, attended the 28 clinics in this study. The mean age was 67 years. There were 240 new patients and 439 follow-up consultations; 190 (28 per cent) patients required ultrasound scans and these were performed immediately by the examining urologist. The indications for scanning are presented in *Table 1*. A Bruel and Kjaer 1846 urological ultrasound machine, fitted with a dual-head, 3 and 5 MHz sector transducer was used for scanning.

Of the 190 patients scanned, 128 had simple bladder residual volume estimations performed immediately after flow rate evaluation. Significant residual urine volumes (>50 ml) were found in 52 of the 128 patients. The remaining 62 patients were scanned for other reasons. The scans were considered positive (50) or negative (12) depending on the presence or absence of detectable pathology (*Table 2*).

The accuracy of the urologist's outpatient scan was assessed by referring these 62 patients for further independent scanning in the radiology department. In all instances the radiologist's

Table 1 *Indications for ultrasonography*

Bladder outflow symptoms	111
Loin pain	21
Haematuria	15
Testicular pathology	13
Miscellaneous	30
Total	190

Table 2 *Positive pathological findings on urologist ultrasound scan in 50 patients*

Organ	No. of cases	Finding
Kidney	17	Hydronephrosis
	9	Cysts
	3	Tumours
	1	Absent kidney
Bladder	4	Tumours
	2	Calculi
	2	Diverticuli
Scrotum	1	Testicular tumour
Other findings (incidental)	6	Gallstones
	2	Ovarian cysts
	1	Aortic aneurysm
	1	Splenic bed cyst
	1	Liver metastases (carcinoma of colon)

scan was in agreement with that of the urologist. There were no false positive or false negative results of clinical significance in the series scanned by the urologist.

Figures provided by Somerset District Health Authority (1987) estimate the average cost of an NHS outpatient clinic appointment at £27, patient transport £12, and formal ultrasound scanning £34. In this district general hospital practice approximately 10 per cent of patients use NHS transport. In the 240 clinics held annually by the department of urology, there is thus a potential theoretical saving of approximately £100 000 per annum if an outpatient ultrasound service is fully implemented (*Table 3*).

Discussion

Although abdominal ultrasound is a skilled radiological technique, the basics of imaging the genito-urinary tract can be readily learned by the urologist. If ultrasound scanning is restricted to the estimation of bladder residual urine volume and the identification of hydronephrosis, the learning period is short. Scanning for these two conditions alone forms the bulk of urological ultrasound requests. The additional time taken to scan a urological patient as part of the outpatient department examination averaged 4 min. This compares favourably with the time taken to write the formal ultrasound request, and to become familiar with the clinical problem when some time has elapsed since the patient was last reviewed.

Table 3 *The economic saving achieved by urologist immediate outpatient ultrasonography based on 190 scans in 28 outpatient clinics*

Item	Cost (£)		Number	Total (£)
Clinic visit	27	×	190	5 130
Formal ultrasound scan	34	×	190	6 460
Transport	12	×	19*	228
Total				11 818
Projected total saving for 240 clinics (1 year)				101 297

Figures based on Somerset District Health Authority, 1987. * It is estimated that 10 per cent of patients use NHS transport

Considerable financial savings can be made by providing outpatient clinical ultrasound facilities (*Table 3*). The basic capital cost of modern ultrasound equipment ranges from £10 000 for an adequate simple scanner to £45 000 for a committed multipurpose sector scanner with rectal and intravesical probes. Moreover, modern ultrasound machines are robust, reliable and portable so that the same machine may be used in the outpatient clinic, in the clinical investigation unit, in the urological ward, and in the operating theatre. The reduced mobility of an elderly population and the anxieties which can be created by the uncertainty of repeated visits to hospital, represent a further advantage for providing an immediate scanning service. Finally, a reduction in the burden of routine work referred to the X-ray department should make the concept of immediate ultrasound attractive to the radiology department.

It is important, however, to recognize the limitations of one's ability and experience, and those of ultrasound itself. Patients must, therefore, continue to be referred for formal departmental ultrasound scanning, plain abdominal radiography, intravenous urography, or isotope renography when clinically indicated if the ultrasound examination is inconclusive.

References

1 Matthews PN, Quayle JB, Joseph AEA, Williams JE, Wilkinson KW, Riddle PR The use of ultrasound in the investigation of prostatism. *Br J Urol* 1982; **54**: 536–8.

2 Vesey SG, Lumb GN, O'Boyle PJ. An evaluation of urologist operated ultrasound and its use in the urological outpatient clinic. *Br J Urol* 1988; **61**. 74–6.

3 Smith H-J, Haveland H. Pre-operative and post-operative volumetry of the prostate by transabdominal ultrasonography. *Br J Urol* 1982; **54**: 531–5

4. Roehrborn CG, Chinn HKW, Fulgham PF, Simpkins KL, Peters PG The role of transabdominal ultrasound in the pre-operative evaluation of patients with benign prostatic hypertrophy. *Urology* 1986; **135**: 1190–3

Paper accepted 11 March 1988

Br. J. Surg. 1988, Vol. 75, September, 923–924

Continuous wound perfusion with bupivacaine for postoperative wound pain

P. Gibbs, A. Purushotham, C. Auld and R. J. Cuschieri

Department of Surgery, Southern General Hospital, Glasgow, UK
Correspondence to: Mr P. Gibbs

Intermittent intramuscular opiates provide unsatisfactory control of pain after abdominal surgery[1]. Recent studies suggest that the intermittent perfusion of subcostal incisions with bupivacaine is associated with good pain relief as determined by linear analogue pain scores[2], and a reduction in postoperative narcotic requirements[3]. There is, however, conflicting evidence regarding the effect on lung function and pulmonary complications[2–4].

The aim of this study was to assess the effect of continuous wound perfusion with bupivacaine on postoperative pain, pulmonary function and respiratory complications after cholecystectomy.

Patients and methods

Eighty patients were studied. The patients were comparable regarding physical characteristics, respiratory status, smoking habits, duration of anaesthesia and operative procedure (*Table 1*). Pre-operative assessment of respiratory status in each patient was established by physical examination, chest radiography, arterial blood gas analysis and measurement of peak expiratory flow rate.

After induction of anaesthesia, intermittent positive pressure ventilation was instituted and anaesthesia maintained by inhalation agents supplemented by intravenous narcotics. All surgery was performed through a right paramedian incision which was closed in layers with a fine epidural catheter (Portex Mini Pack Epidural System) being placed between peritoneum and rectus muscle and brought out through the wound. The catheter was connected to a disposable bacterial filter and the system flushed with 10 ml saline. Patients were randomly allocated to receive 150 ml of either 0·5 per cent bupivacaine or normal saline over 60 h by continuous infusion using a Vickers medical syringe pump. During this period intramuscular morphine was available on demand if pain relief was inadequate. One patient in the saline group required further surgery and was excluded from further study.

Pain was assessed twice daily using a standard 100 mm linear analogue scale[5]; patients were asked to record their average pain over each 12 h period. Morphine requirements were noted. Arterial blood gas analysis, followed by measurement of peak expiratory flow rate, was carried out on the first, second and fourth postoperative days. Patients were assessed daily for the development of pulmonary complications[6]. Wounds were examined daily for the development of infection.

Table 1 *Comparison of patient characteristics between groups*

Patient characteristics	Normal saline ($n=39$)	Bupivacaine ($n=40$)	
SexM:F	4:35	7·33	n s.
Mean age (years)	47 (22–79)	52 (17–83)	n s.
Mean height (cm)	160 (147–177)	160 (147–175)	n.s
Mean weight (kg)	64 (39–95)	65 (41–83)	n.s
Smokers	15	14	
Mean duration of anaesthesia (min)	61 (25–150)	60 (20–205)	n.s
Common duct exploration	8	5	n s

Values in parentheses are ranges

Results

There was no significant difference in the severity of pain as measured by linear analogue pain scores between the groups (*Table 2*). The mean morphine requirements over the first 48 h were 60 mg (range 15–100 mg) for the saline group and 52 mg (range 10–100 mg) for the bupivacaine group (n.s.). There was no significant difference between the two groups in arterial oxygen tensions both before surgery and during the first 4 postoperative days (*Table 3*). Likewise, there was no significant difference in peak expiratory flow rates (*Table 4*). Eight patients in the bupivacaine group developed chest infections compared with seven in the saline group (n.s.). No wound infections were noted.

Discussion

The direct perfusion of surgical wounds with local anaesthetic was first shown more than 30 years ago to reduce opiate requirements after abdominal surgery[7], but fear of potential

Table 3 *Mean (±s.e m.) arterial oxygen tensions (mmHg)*

	Pre-operative	Postoperative Day 1	Postoperative Day 2	Postoperative Day 4
Saline ($n=39$)	88±2	69±2	69±2	80±2
Bupivacaine ($n=40$)	91±2	71±2	69±2	78±2
P value	n.s.	n s.	n s.	n.s.

Table 4 *Mean peak expiratory flow rate (l/min)*

	Pre-operative	Postoperative Day 1	Postoperative Day 2	Postoperative Day 4
Saline ($n=39$)	369 (200–550)	135 (50–260)	152 (50–270)	249 (70–350)
Bupivacaine ($n=40$)	378 (150–680)	143 (60–325)	172 (50–380)	252 (100–550)

Values in parentheses are ranges

Table 2 *Mean linear analogue pain scores in millimetres*

	Day 1 a.m.	Day 1 p m.	Day 2 a m.	Day 2 p m.	Day 3 a m	Day 3 p.m.	Day 4 a.m	Day 4 p m
Normal saline ($n=39$)	61 (10–96)	53 (4–88)	44 (4–88)	42 (5–90)	33 (3–78)	33 (3–90)	26 (0–75)	20 (0–65)
Bupivacaine ($n=40$)	53 (13–96)	52 (14–95)	44 (14–95)	38 (3–85)	32 (3–76)	27 (0–70)	25 (0–90)	19 (0–80)

Values in parentheses are ranges

0007-1323/88/090923–02$3 00

infection and delayed wound healing prevented the technique from becoming universally adopted. The introduction of longer acting local anaesthetic drugs, such as bupivacaine, and the development of bacterial filters has led to renewed interest in this method of postoperative pain relief. Thomas *et al.*[3] showed that the perfusion of subcostal incisions with bupivacaine via an indwelling catheter inserted beneath the rectus sheath was associated with a reduction in narcotic requirements but had no effect on postoperative pulmonary mechanical function. In contrast Patel *et al.*[4] using a single injection of bupivacaine into the wound after cholecystectomy demonstrated a lesser reduction in forced vital capacity and forced expiratory volume (1 min) compared with controls. More recently Levack *et al.*[2] showed that intermittent infusion of subcostal wounds with bupivacaine was associated with lower linear analogue pain scores when compared with infusion with saline.

Our findings are at variance with previous studies despite the use of a similar technique of wound perfusion. However, these studies have been based on small samples[3,4], did not contain a homogeneous group[2] and often referred to the effect of a bolus injection of bupivacaine into the wound[2,4]. In the study by Thomas *et al.*[3] the reduction in analgesia requirement in the bupivacaine group may have been the result of a placebo effect as the control group did not have an indwelling catheter.

In this study, continuous infusion of bupivacaine into upper abdominal wounds did not produce better pain relief than perfusion with normal saline, neither did it influence the incidence of postoperative pulmonary complications. We feel that further studies are indicated before wound perfusion with bupivacaine can be accepted as a valid method of postoperative pain relief after upper abdominal surgery.

References

1. Dodson MA A review of the methods of relief of post-operative pain. *Ann R Coll Surg Engl* 1982, **64**: 324–7.
2. Levack ID, Holmes JD, Robertson GS. Abdominal wound perfusion for the relief of post-operative pain *Br J Anaesth* 1986; **58**. 615–19.
3. Thomas DFM, Lambert WG, Lloyd-Williams K. The direct perfusion of surgical wounds with local anaesthetic solution: an approach to post-operative pain? *Ann R Coll Surg Engl* 1983, **65**: 226–9
4. Patel, JM, Lanzafame RJ, Williams JS, Mullen BV, Hinshaw JR The effect of incisional infiltration of bupivacaine hydrochloride on pulmonary function, atelectasis and narcotic need following elective cholecystectomy. *Surg Gynecol Obstet* 1983; **157**: 338–40.
5. Revill SI, Robinson JO, Rosen M, Hogg MIS. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976, **31** 1191–8
6. Cuschieri RJ, Morran CG, Howie C, McArdle CS. Postoperative pain and pulmonary complications—comparison of three analgesic regimens. *Br J Surg* 1985; **72**. 495–8.
7. Lewis DL, Thompson WAL. Reduction of post-operative pain *Br Med J* 1953; **1** 973–4.

Paper accepted 13 March 1988

Br. J. Surg. 1988, Vol. 75, September, 924–925

Oral pancreatic enzymes accelerate closure of external pancreatic fistulae

A. M. García-Pugés, S. Navarro, L. Fernández-Cruz, E. Ros, L. Hinojosa and C. Pera

Gastroenterology Service and Department of Surgery, Hospital Clínic i Provincial, University of Barcelona, Spain

Correspondence to. Dr A. M. García Pugés,
Servicio de Gastroenterologia, Hospital Clínic i Provincial,
c/ Casanova, 143, 08036 Barcelona, Spain

High-output pancreatic fistulae carry a high morbidity and mortality owing to fluid and electrolyte losses, protein–calorie malnutrition, and an increased risk of infection. The suppression of physiological pancreatic stimulation by complete fasting and total parenteral nutrition (TPN) is central to the medical management[1]. Glucagon and somatostatin have also been used[2,3].

Feedback inhibition of exocrine pancreatic secretion by pancreatic enzymes in the duodenal lumen has been demonstrated in animals[4,5], healthy man[6–8] and patients with chronic pancreatitis[9,10]. We have explored the possibility of inhibiting exocrine pancreatic secretion by oral administration of pancreatic proteases with the object of speeding the closure of pancreatic fistulae.

Patients and methods

Five consecutive patients with postoperative external pancreatic fistula were studied. Sinus tracts communicating with the main pancreatic duct were documented in all cases by either fistulography or endoscopic retrograde pancreatography (*Table 1*).

After a period of 2–4 days fasting and intravenous parenteral nutrition, TPN was started in all patients, through a central venous catheter, and continued for 17–31 days After this an oral pancreatic enzyme preparation (Pankreon Fuerte®, Kalifarma Lab , providing lipase, 5557±1811 units/l trypsin 30±4 units/l, chymotrypsin 360±145 units/l, and dispersed bovine bile, 75 mg per tablet) was added at a dose of four tablets every 6 h and cimetidine 200 mg was given with each dose

Fistula flow and trypsin concentration[11] were measured daily until complete closure of the fistulae.

Table 1 *Clinical data, type of operation, and basal flow and trypsin concentration from external pancreatic fistula in five patients*

					Fistula	
Patient	Sex	Age	Diagnosis	Surgical procedure	Flow (ml/day)	Trypsin (units/l)
1	M	63	Acute pancreatitis, pancreatic ascites	Subtotal pancreatectomy	800	39 000
2	M	38	Chronic pancreatitis	Subtotal pancreatectomy	610	38 000
3	M	35	Chronic pancreatitis	Pancreaticojejunostomy	420	11 000
4	M	57	Congenital hepatic fibrosis, bleeding oesophageal varices	Oesophageal transection + splenectomy	370	5000
5	M	38	Chronic pancreatitis	Subtotal pancreatectomy	220	4200

Table 2

Patient	Intravenous fluids and electrolytes (days)	TPN* (days)	Mean fistula flow during TPN 3-day interval (ml)	TPN plus oral pancreatic enzymes until fistula closure (days)
1	4	17	800, 610, 630, 650, 630, 615	3
2	2	31	600, 610, 600, 620, 590, 410, 420, 430, 420, 430, 430	1
3	4	21	400, 400, 290, 280, 210, 200, 210	4
4	4	30	390, 390, 320, 300, 230, 250, 230, 220, 230, 230	12
5	4	21	220, 210, 200, 190, 180, 185, 180	3

* TPN, total parenteral nutrition composition: nitrogen (13–16 g), glucose (250–300 g), long-chain triglycerides (50–100 g), vitamins and trace elements

Results

Basal fistula flow and trypsin concentration in the five patients were (mean ± s.d.) 484 ± 201 ml/day, and 19 940 ± 15 742 units/l, respectively. At the end of 5 days of TPN (before pancreatic enzymes were started), flow and trypsin concentration had decreased to approximately one-half of basal values (249 ± 102 ml/day, and 12 250 ± 10 497 units/l, respectively). After administration of pancreatic enzymes, both fistula flow and trypsin concentration were rapidly reduced and fistulous flow ceased completely at between 1 and 12 days, with ensuing closure of the sinus tract. The patient in whom the fistula took longer to heal was the one with congenital hepatic fibrosis and portal hypertension, and he had moderate ascites throughout his hospitalization (*Table 2*).

The sinus tracts from the pancreatic fistula remain closed in all five patients after a mean follow-up of 9 months (range 4–17 months).

Discussion

The utilization of oral pancreatic enzymes in patients with pancreatic fistula associated with TPN has been unreported so far. The useful effect of this therapy on the five patients reported here was a sudden fall of fistulous flow (*Table 2*) with a parallel marked decrease of trypsin concentration. These observations suggest that the mechanism of this effect is an inhibition of exocrine pancreatic function, and support the recently postulated existence of a feedback control of pancreatic secretion by intraduodenal enzymes[6,7].

The present experience suggests that this simple, safe and inexpensive treatment might considerably shorten the duration of parenteral nutrition and hospitalization, thereby reducing both morbidity and costs in patients with this infrequent but serious postoperative complication.

References

1. Thomas RJS The response of patients with fistula of the gastrointestinal tract to parenteral nutrition *Surg Gynecol Obstet* 1981; **153**. 77–80.
2. Shapiro H, Ludewig R The effect of glucagon on the exocrine pancreas. *Am J Gastroenterol* 1978, **70** 274–81
3. Di Constanzo J, Cano N, Martin J Somatostatin in persistent gastrointestinal fistula treated by total parenteral nutrition. *Lancet* 1982, **ii**: 338.
4. Greene GM, Lyman RL Feedback regulation of pancreatic enzyme secretion as mechanism for trypsin inhibitor induced hypersecretion in rats. *Proc Soc Exp Biol Med* 1972, **140**· 6–12
5. Ihse I, Lilja P Effects of intestinal amylase and trypsin on pancreatic secretion in the pig. *Scand J Gastroenterol* 1979; **14**. 1009–13.
6. Ihse I, Lilja P, Lundquist I. Feedback regulation of pancreatic enzyme secretion by intestinal trypsin in man *Digestion* 1977, **15**· 303–8.
7. Osnes M, Hanssen LE. The influence of intraduodenal administration of pancreatic juice on the bile-induced pancreatic secretion and immunoreactive secretin release in man. *Scand J Gastroenterol* 1980, **15**: 1041–7.
8. Jacobson D, Tielman R, Toskes P, Currington C Acute and chronic feedback inhibition of pancreatic exocrine secretion in human subjects. *Gastroenterology* 1982; **82**. 1091 (abstract).
9. Slaff J, Jacobson D, Tielman R, Currington C, Toskes P. Protease-specific suppression of pancreatic exocrine secretion *Gastroenterology* 1984, **87**: 44–52.
10. Isaksson G, Ishe I. Pain reduction by an oral pancreatic enzyme preparation in chronic pancreatitis *Digest Dis Sci* 1983, **28**. 97–102.
11. Erlangen B, Kokowsky N, Cohen W The preparation and properties of two new chromogenic substrates of trypsin *Arch Biochem* 1961; **95**: 271–7.

Paper accepted 11 March 1988

British Association of Endocrine Surgeons

The Annual Meeting of the British Association of Endocrine Surgeons was held at the University of Wales College of Medicine, Cardiff, UK on 20 May 1988

Parathyroid hormone related peptide production by tumours and normal epithelial tissues

D.A. Heath, H.M. Docherty, P. Milton and M. Dixon-Lewis, *Department of Medicine, Queen Elizabeth Hospital, Birmingham, UK*

Many of the biochemical and histological changes in hypercalcaemic malignancy and hyperparathyroidism are similar. The production of parathyroid hormone (PTH) by non-parathyroid tumours now appears to occur either very rarely or not at all, yet there is much evidence to suggest that a PTH-like factor is produced. We have studied a human carcinoid tumour associated with severe hypercalcaemia, subperiosteal erosions and osteitis fibrosa cystica Extracts of the tumour contain factors which are very active in a PTH bioassay system—the rat osteosarcoma cell assay This activity could not be blocked by various PTH antibodies but was abolished by a PTH-receptor antagonist Factors with similar biological activity have been identified from a variety of other malignancies by other workers and the gene for this factor has been cloned and shown to code for a peptide of 141 amino acids with some structural similarities to PTH. We have raised antibodies to synthetic PTH-related peptide (PRP) and have shown that they inhibit the activity of the carcinoid tumour extract.

In separate studies we have shown that normal human keratinocytes, as well as a variety of other cells of epithelial origin, contain or secrete PRP. PTH and/or PRP receptors are present on skin fibroblasts. PRP therefore appears to be a normal factor produced by many epithelial cells with probable paracrine actions. When produced in excess by tumours it may be the cause of the hypercalcaemia of malignancy.

Renal function in primary hyperparathyroidism: pre-operative and postoperative evaluation with five different tests

A. Kristoffersson, C. Backman, K. Grankvist and J. Jarhult, *Departments of Surgery, Clinical Physiology and Clinical Chemistry, University Hospital, Umea, Sweden*

Impaired renal function is a well-known complication of primary hyperparathyroidism (HPT). The incidence and severity of this impairment vary considerably in different reports.

Owing to the changing panorama of HPT during the last decades, we were interested to find out whether today's patients suffer from renal damage and whether a depression of renal function can be reversed by surgery.

Patients. Investigations were carried out on 19 consecutive patients, 15 women and 4 men with median age 61 years (range 39–71), immediately before and 12 months after parathyroidectomy. All patients had an adenoma removed and were normocalcaemic at follow-up.

Methods The following tests on renal function were performed on both occasions· plasma creatinine, creatinine clearance, ^{51}Cr-labelled EDTA clearance, U-beta-2- microglobulin and desmopressin test

Results Four patients had slightly elevated levels of plasma creatinine pre-operatively Two patients had abnormally low values of creatinine clearance before operation and four had reduced clearance measured with ^{51}Cr-labelled EDTA Normal pre-operative values of β_2-microglobulin were found in all but two patients. Fourteen patients had a depressed concentrating capacity before the parathyroidectomy.

One year after parathyroidectomy no significant changes in plasma creatinine, creatinine clearance. ^{51}Cr-labelled EDTA clearance or β_2-microglobulin were found for the whole group Complete normalization of concentrating capacity had occurred in 7 of 14 patients, improvement was registered in 9 patients, 1 patient was unchanged while a slight impairment was noticed in 2. For the whole group a significant improvement had occurred ($P < 0\cdot004$).

In conclusion, impaired renal function as assessed by creatinine or creatinine clearance is uncommon among HPT patients today. Distal tubular function, however, is often depressed and can be positively influenced by surgery. More sensitive tests, such as desmopressin and possibly ^{51}Cr-labelled EDTA clearance, are suggested to test for early impairment of renal function in HPT.

Investigations on the secretion of parathyroid hormone using a new two-site immunochemiluminometric assay specific for intact parathyroid hormone

R.C. Brown, J.P. Aston, J.S. Woodhead, P.A. Lucas*, I.R. Curley†, B. Harrison† and M.H. Wheeler, *Departments of Medical Biochemistry, *Renal Medicine and †Surgery, University of Wales College of Medicine, Cardiff, UK*

The majority of circulating parathyroid hormone (PTH) is biologically inert carboxy terminal fragments ($t_{\frac{1}{2}} > 1$ h), and only a relatively small proportion is the biologically active intact peptide ($t_{\frac{1}{2}} < 5$ min) This heterogeneity has presented considerable difficulties in the design and interpretation of PTH immunoassays because of poor sensitivity, lack of specificity and overlap of serum values in normal subjects and patients. We have developed a sensitive immunochemiluminometric assay (ICMA) specific for intact PTH. Circulating concentrations (pmol/l) for normals and for patients with surgically proven primary hyperparathyroidism (HPT), chronic renal failure (CRF), hypoparathyroidism (HYPO) and malignancy associated hypercalcaemia (MAHC) are given in the table.

	Normals	HPT	CRF	HYPO	MAHC
n	82	55	20	4	17
Mean	3·4	23·4	17·8	<0·8	<0·8
Range	1·2–9·4	9·0–200	2·2–83	<0·8	<0·8–5·2

Because the assay measures the secreted intact peptide rather than the products of peripheral metabolic cleavage, the usefulness of dynamic stimulation/suppression tests has been investigated Repeated rapid sampling at 3-min intervals has indicated no pulsatile secretion pattern. In normals, oral (1·2 g bolus) and intravenous (2·5 mg/kg over 30 min) calcium administration resulted in suppression (<0·8 pmol/l) of circulating intact PTH; this was not observed in hyperparathyroidism and renal failure patients Intramuscular calcitonin (100 units) induced a rise in PTH in patients with hyperparathyroidism at 120, 180 and 240 min. Studies on the secretion of intact PTH from dispersed human hyperparathyroid cells *in vitro* have indicated that suppression at high Ca^{2+} (2·5 mM) and secretion rate at low Ca^{2+} (0·5 mM) of hyperplastic tissue was greater ($P < 0\cdot05$, $P < 0\cdot01$, respectively) than adenomatous tissue.

It is concluded that the intact PTH ICMA provides greater diagnostic efficiency than previous PTH fragment assays and is an important tool for the investigation of the secretory physiology of parathyroid tissue.

0007–1323/88/090926–05$3 00

Hyperparathyroidism following neck irradiation

T.J. Christmas, C.R. Chapple, E.J.G. Milroy and A.G.A. Cowie, *Department of Urology, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK*

Between 1900 and 1950 radiotherapy was often used in the treatment of benign conditions of the neck such as tuberculous adenitis, acne, hirsutism, goitre, tonsillitis and skin lesions. An increase in the incidence of neoplasms of the skin and parotid and thyroid glands has been shown in these patients, often more than 30 years later. Parathyroid adenomas have been induced experimentally in rats by the administration of ^{131}I.

A retrospective review of 1550 cases of hyperparathyroidism (HPT) reveals a history of neck irradiation in nine cases (0·6 per cent). External beam therapy alone was used in four, ^{131}I alone in two, both external beam therapy and ^{131}I in two, and radium wire implants in one case. The mean interval between radiation exposure and the development of HPT was 37 years (range 9–63 years). The indication for radiotherapy was thyroid disease in five, cervical tuberculosis in three, and a benign skin lesion in one case. All patients were markedly hypercalcaemic at presentation with parathyroid hormone levels exceeding 160 pg/ml, and all underwent parathyroidectomy. The parathyroid histology was adenoma in six, carcinoma in two and nodular hyperplasia in one case Apart from one patient who had previously undergone total thyroidectomy for papillary carcinoma, all had coincident thyroid disease consisting of nodular colloid goitre in seven and follicular carcinoma in one case. The significance of these findings is discussed.

Aspects of osteomalacia associated with primary hyperparathyroidism: 7 cases from a series of 500 primary hyperparathyroidism

C. Proye, A. Richardson, B. Grardel, A. Thevenon, B. Duquesnoy, J.L. Quievreux, J.L. Wemeau, M. Decoulx, J. Lefebvre and B. Delcambre, *Surgical Professorial Unit, University Hospital of Lille, France*

The types of osteomalacia associated with primary hyperparathyroidism (HPT) have been known since 1956. However, reported cases are rare and the pathophysiology is poorly understood. The criteria for diagnosis include: normal renal function, - proven parathyroid adenoma(s), radiological or histological osteomalacia Amongst 500 cases of proven primary HPT operated in Lille, 7 were associated with osteomalacia (1·4 per cent). There were six women and one man The average age of patients was 57 years (range 34–74). The clinical and radiological manifestations were: juvenile pseudorickets (one case); Looser–Milkman striae (four cases) with normocalcaemic florid fibrocystic osteitis (two cases), parathyroid crisis (one case), haemochromatosis associated with HPT (one case); incidental finding on bone biopsy (two cases)

Hypercalcaemia was not always present (5/7 cases) whereas hypophosphatemia always was (7/7). Alkaline phosphatase was elevated in 3 of 7 cases. PTH level when determined was elevated or inappropriate in all cases (6/6). In six cases 25-OH vitamin D was low and the vitamin D test was positive in the seventh patient. On bone biopsy (five cases), the thickness index of osteoid seams was increased, and the calcification rate was decreased. A single adenoma was removed in all seven cases, and the five hypercalcaemic patients have been normocalcaemic since then. In the two cases of normocalcaemia, another cause of vitamin D deficiency was found (1 bedridden, 1 taking barbiturates). In the hypercalcaemic cases, the role of hypophosphataemia (5/5) and that of an endogenous, HPT-induced vitamin D deficiency were discussed One case may have corresponded to a primary osteomalacia because the vitamin D level was still low 10 years later.

The frequency of osteomalacia associated with primary HPT is probably underestimated in the absence of routine bone biopsy. An exogeneous vitamin D deficiency may mask the hypercalcaemia and be responsible for the most severe forms.

Management of hyperparathyroidism in pregnancy

J.S.K. Gelister, J. Sanderson, C.R. Chapple, T. Christmas, J. O'Riordan, A.G.A. Cowie and E.J.G. Milroy, *Departments of Endocrinology and Urology, University College and Middlesex Hospital, London W1N 8AA, UK*

Hyperparathyroidism (HPT) associated with pregnancy is uncommon It has been suggested that all such patients should undergo neck exploration during pregnancy. Therefore, from our series of 1550 patients with HPT, 15 associated with pregnancy have been reviewed.

In ten women HPT was diagnosed postpartum after symptomatic neonatal hypocalcaemia. Diagnosis preceded pregnancy in one woman and was made during pregnancy in the others. Two patients were explored during pregnancy. In one, four normal glands were found and hypercalcaemia persisted; after a successful pregnancy a mediastinal adenoma was removed. Exploration in the second woman, precipitated by severe hypercalcaemia, revealed four hyperplastic glands A normocalcaemic pregnancy ensued

A single adenoma was removed from ten patients and two adenomata from an eleventh. Four-gland hyperplasia was discovered in one patient, four normal glands only in one other, and two patients had parathyroid carcinoma.

Of twenty hypercalcaemic pregnancies in this series there was one stillbirth associated with severe hypercalcaemia secondary to parathyroid carcinoma. Surgical exploration during pregnancy is indicated for severely hypercalcaemic patients. In less severe cases the risks of neck exploration in pregnancy must be weighed against those of neonatal tetany.

Thyroglobulin measurement in the follow-up of differentiated thyroid carcinoma after lobectomy

R.D. Harvey*, A. Rodgert†, P.S. Grabowski*, N.A. Matheson and R.L. Himsworth, *Departments of Medicine, *Therapeutics and †Surgery, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD, UK*

Thyroglobulin (Tg) measurement is well established for the detection of tumour recurrence after total thyroidectomy for thyroid cancer, but its utility in the follow-up of patients treated by lobectomy has not been reported. We have measured Tg in 52 patients treated by lobectomy and subsequent thyroxine to suppress TSH secretion All the patients had differentiated carcinomas and included two with recurrent tumour. The median duration of follow-up was 4·5 years

Tg measured by radioimmunoassay was $<10\,\mu$g/l (mean $3\,\mu$g/l) in 86 of a total of 114 samples. All 86 samples were from patients without clinical recurrence or thyroiditis histologically, and the thyroglobulin auto-antibody (TgAb) titre, by ELISA, was $<1/20$ in all but one TSH by immunoradiometric assay was detectable ($>0\cdot1$ milliunits/l) in 29 of the 86 samples (median 0·55 milliunits/l, range 0·11–2·0 milliunits/l)

In the seven samples from the two patients with metastases, mean serum Tg was 41 and 225 μg/l respectively despite TSH suppression ($<0\cdot1$ milliunits/l) Serum Tg was $>10\,\mu$g/l (median 22 μg/l, range 12–81 μg/l) in fourteen samples from nine patients in whom either TSH was $>1\cdot0$ milliunits/l, histology showed thyroiditis, the TgAb titre was $>1/20$, or the interval since surgery was <2 months In seven samples from six patients, Tg was $>10\,\mu$g/l (median 17 μg/l, range 11–33 μg/l) for no evident reason.

Serum Tg measurement is of value in the detection of recurrence of differentiated thyroid cancer after lobectomy, provided suppressive thyroxine is given and the possibility of interfering Tg auto-antibodies or thyroiditis has been excluded. In our series there were no false negative results. The six patients with an unexplained elevation of Tg may have occult recurrence, or represent true false positive results.

Pre-operative parathyroid localization in three dimensions

B.J. Jenkins, M.S. Newell, A.W. Goode, B.J. Boucher, J.P. Monson and C.L. Brown, *The London Hospital, Whitechapel, London E1, UK*

A limitation to thallium–technetium subtraction scintigraphy in patients with primary hyperparathyroidism has been the inability to obtain an image in a third plane, making it difficult to assess the depth of an abnormal gland in the neck. In an attempt to overcome this problem, a new technique has been developed that provides transaxial sections of the scintigram, thereby giving a representation of parathyroid tissue in a third dimension.

After conventional subtraction scanning, information from both thallium and technetium energy windows is acquired in 64 positions by a rotating γ camera and stored on a computer. Data are then processed by standard filtered back projection methods resulting in two sets of equivalent transaxial slices representing the simultaneous distribution of thallium and technetium in the neck which are subtracted in a similar way to planar images.

In eight patients with primary hyperparathyroidism undergoing initial cervical exploration, a positive two-dimensional subtraction scan indicating the presence of a single adenoma was followed by successful surgery and return of the serum calcium to normal. In six of these patients emission tomography gave a precise image representing the position of the adenoma in the anteroposterior plane

Early results with scintigraphic tomography suggest that it may be used to obtain an image of a parathyroid adenoma in a third plane. Greater experience is required to determine if the technique is useful in patients with multigland hyperplasia or those with persistent or relapsed hyperparathyroidism.

Prognostic value of DNA aneuploidy in papillary thyroid cancer: a comparison of static densitometry and flow cytometry

E.L. Cusick, C.A. MacIntosh, Z.H. Krukowski, S.W.B. Ewen and N.A. Matheson, *Departments of Surgery and Pathology, University of Aberdeen, Aberdeen, UK*

DNA aneuploidy may be an independent prognostic factor in malignancy The evidence in various tumours is conflicting but in papillary thyroid carcinoma DNA aneuploidy has been found to be a highly significant prognostic factor[1].

The prognostic accuracy of flow cytometric and static densitometric DNA analysis was compared in 34 patients who had undergone surgery for papillary thyroid cancer between 1959 and 1978 (median follow-up 18 years). Static densitometry was performed on thin paraffin sections and flow cytometry on disaggregated thick paraffin sections. technically satisfactory preparations were made in 31 cases

Five patients died of thyroid cancer Three of six patients found to have DNA aneuploid tumours by flow cytometry died of thyroid cancer ($P<0{\cdot}05$, Fisher's exact test) compared with four of eight patients found to be aneuploid by static densitometry ($P<0{\cdot}02$). In contrast, quantitative static densitometry correctly identified all five patients dying of cancer with no false positives ($P<0{\cdot}002$).

The presence of non-tumour cells is a limiting factor in the accuracy of flow cytometric measurement of the percentage of DNA aneuploid tumour nuclei and is less accurate than static densitometry in which morphological selection of malignant cells permits quantitative measurements increasing the prognostic accuracy

1. Cohn K, Backdahl M, Forsslund G *et al.* Prognostic value of nuclear DNA content in papillary thyroid carcinoma. *World J Surg* 1984; **8**: 474–80

Aspiration cytology for goitres: further trials and triumphs

A.J. Webb, *Department of Surgery, The Royal Infirmary, Bristol, UK*

The diagnostic sensitivity of fine needle aspiration biopsy (FNAB) for 53 follicular neoplasms arising within 500 patients with goitre was presented to the Association in 1986. Problems found during this retrospective investigation required a more detailed study with specific attention to cytological difficulty

During 1986 and 1987 a prospective investigation has developed incorporating a tighter protocol and more precise cytological reporting Preliminary results are presented. In all, 105 patients were referred, from whom 163 cytological biopsies were derived (144 FNAB and 19 operative smears), 66 patients received surgery

The results confirmed the acceptable sensitivity of cytology for proving thyroid neoplasm (28/30 cases) at 93 per cent. For follicular adenoma, of which 35 per cent were cystic, the sensitivity was 19/21 (90 per cent). For the total series, the specificity of cytology for neoplasm was 98 per cent.

Nevertheless, some areas of cytological uncertainty stand out and 9 of 30 (30 per cent) of the proven neoplastic lesions and 9 of 73 (12 per cent) of the non-neoplastic cases were diagnostic problems. The specific areas of difficulty are:

1. The identification of neoplasm within a clinically and ultrasonically solitary cystic lesion[1,2]
2. The distinction between a hyperplastic nodular area and follicular adenoma
3. The tumour-like areas of discrete Hurthle cell hyperplasia within atypical lymphoid thyroiditis which mimic Hurthle cell adenoma
4. The distinction between atypical follicular adenoma and carcinoma; perhaps some follicular neoplasms should be designated 'borderline', especially where histopathological opinions are sharply divided
5. The recognition of neoplasm within a clinically and scintiscan-substantiated nodular goitre.

The tentative conclusions are:

1. Clinical mistakes in the assessment of solitary thyroid nodules can be serious and FNAB will prevent persisting error
2. FNAB can mostly attain greater precision than scanning investigations
3. Perhaps, in the problem group, the cytologists should attempt no more than to warn the surgeon of the possibility of neoplasm.

1. Rosen IB, Provias JP, Walfish PG Pathologic nature of cystic thyroid nodules selected for surgery by needle aspiration biopsy. *Surgery* 1986; **79**: 606–11
2. Hammer M, Wortsman J, Folse R. Cancer in cystic lesions of the thyroid. *Arch Surg* 1982; **117**: 1020–3.

Diagnostic value of four thyroid screening methods

K.J. Manolas, V. Primikiris, N. Lyrantsopoulos, P. Kalofolias and D. Baxevanides, *Department of Surgery, University of Thrace Medical School and University and District Hospital of Alexandroupolis, Greece*

In this prospective clinical study, the diagnostic values of the four methods which are routinely used in diagnosing the thyroid diseases (clinical examination, thyroid scanning, ultrasonography and fine needle aspiration (FNA)) were evaluated (solely and in all combinations).

The pre-operative clinical diagnosis on which they were based was subsequently compared with the histological diagnosis of the surgical specimen (final diagnosis) and was regarded as 'correct', 'wrong' or 'doubtful', accordingly.

A total of 122 patients (19 men, 103 women) with a mean age of 48·2 years were included FNA achieved the highest correct score (45/65, 69 per cent) and the clinical examination the lowest one (24/122, 20 per cent). The thyroid scanning and the ultrasonography yielded equal levels of correct (32·0–33·5 per cent) and wrong (24·5–

25·0 per cent) results. FNA had the lowest percentage of doubtful diagnoses (3/65, 5 per cent) and clinical examination had the highest (70/122, 57 per cent). All the above differences were found to be statistically highly significant ($\chi^2=56{\cdot}48$, $P=0{\cdot}5\times10^{-7}$).

From the combinations where two methods were involved, the highest correct and, at the same time, the lowest wrong and doubtful results were obtained when clinical examination and FNA were used (45/65, 69 per cent; 17/65, 26 per cent, 3/65, 5 per cent respectively) ($\chi^2=15{\cdot}35$, $P<0{\cdot}01$).

From the combinations where three methods were diagnostically involved, it was found that clinical examination plus thyroid scanning plus FNA yielded the highest correct (45/64, 70 per cent) results and the lowest wrong and doubtful results (18/64, 28 per cent and 1/64, 2 per cent respectively) ($\chi^2=12{\cdot}78$, $P<0{\cdot}025$). When the best combination of two methods was compared with the best one of three, the recorded difference was not statistically significant.

Also, it was found that FNA as a sole method achieved a 69 per cent correct diagnostic result in this series; the diagnostic ability of FNA did not improve when combined with other methods.

Bio-active prolactin in breast cancer

P.R. Maddox, D.L. Jones and R.E. Mansel, *University Department of Surgery, University of Wales College of Medicine, Cardiff, UK*

The pivotal role of prolactin (PRL) in the development and growth of rodent mammary tumours is now well established, but there remains some controversy on the role of the hormone in human breast cancer. The conflicting results to date have used radioimmunoassays (RIA) to measure serum PRL, which may not necessarily reflect the biological activity of the hormone

We have developed a new microbioassay (BA) for PRL and growth hormone, based on the mitogenicity of lactogenic hormones for the rat Nb2 lymphoma cell line[1], to examine prolactin bio-activity in breast disease.

Serum prolactin levels by both BA and RIA were determined in 31 patients with breast cancer Basal levels and peak responses to thyrotropin releasing hormone were evaluated Serum PRL by BA was found to be significantly greater than RIA for both mean basal* (BA 10·2 ng/ml, RIA 4·7 ng/ml) and mean peak-thyrotropin releasing hormone† (BA 68·6 ng/ml, RIA 37·0 ng/ml) levels, giving a mean BA:RIA ratio of 2·5 and 2·2 for basal and peak-thyrotropin releasing hormone levels respectively

These results indicate that variant non-immunogenic forms of prolactin (or enhancing serum factors) may be present in the sera of patients with breast cancer, causing increased biological activity, and suggests that previous attempts to assess the importance of PRL in breast cancer by RIA may have failed to measure this biologically important activity

* $P<0{\cdot}00001$; † $P<0{\cdot}001$ (BA *versus* RIA, Mann–Whitney *U* test)

1. Tanaka T *et al.* A new sensitive and specific bioassay for lactogenic hormones: measurement of prolactin and growth hormone in human serum. *J Clin Endocrinol Metab* 1980; **51**. 1058–63

The most useful investigation in the initial assessment of Cushing's syndrome

J.P. Monson, G. Koios, G.C. Toms, P.G. Kopelman, B.J. Jenkins, A.W. Goode and T.T. King, *Medical Unit (Endocrinology), Surgical Unit and Department of Neurosurgery, London Hospital and Medical College, London E1 1BB, UK*

Computerized tomography (CT) is now routinely used in the investigation of Cushing's syndrome. The results obtained prompt a re-appraisal of the relative value of other diagnostic investigations. We have therefore examined the diagnostic contribution of high-dose dexamethasone suppression, plasma ACTH and adrenal CT in a consecutive series of 23 patients with Cushing's syndrome. Seven patients failed to demonstrate suppression of plasma and urine free cortisol with dexamethasone, of whom two had recordable plasma ACTH levels on repeated samples (14–58 ng/l). A unilateral adrenal abnormality was evident in these seven patients on abdominal CT Autonomous adrenal function was confirmed in the five patients who underwent selenocholesterol scanning and an adrenal adenoma was surgically removed in all seven patients. The remaining 16 patients demonstrated >50 per cent suppression with dexamethasone, measurable plasma ACTH (23–200 ng/l) and a symmetrical appearance on adrenal CT (performed in 14 patients, normal size in 11, minimal enlargement in 3). Of the 16 patients, 9 demonstrated pituitary CT abnormalities (3 macro-adenomas, 6 micro-adenomas) Eight of these patients and one other were treated by trans-sphenoidal surgery with histological confirmation in all. Three patients experienced resolution of cortisol excess from external pituitary irradiation (DXT) only, three patients underwent initial DXT and bilateral adrenalectomy and one patient DXT and long-term metyrapone therapy. Pituitary-dependent Cushing's syndrome was thus proved in 12 patients and considered probable in the remaining 4 who had no radiological or clinical features to support low-grade ectopic ACTH production (follow-up range 3–5 years). The findings confirm previous reports that dexamethasone suppression tests, ACTH measurements and adrenal CT provide similar information in distinguishing adrenal and ACTH-dependent Cushing's syndrome. The investigation of documented cortisol excess should begin with adrenal CT. A focal abnormality, if confirmed with autonomous function on selenocholesterol scanning, obviates the need for further endocrine investigation

Immunosuppressed canine islet autografts and allografts maintain metabolic normality

A.J. Guy, S.M. Griffin, D. Alderson and J.R. Farndon, *Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne, UK*

If islet transplants restored metabolic normality to diabetic patients, secondary complications could be prevented The effectiveness of immunosuppressed (cyclosporin A (CsA) 20 mg kg^{-1} day^{-1}) canine intrasplenic islet auto- and allografts has been investigated in pancreatectomized beagles, in four groups: controls (group 1, $n=65$), islet autografts (group 2, $n=9$), islet autografts+CsA (group 3, $n=6$), islet allografts+CsA (group 4, $n=5$). Metabolic assessment was by intravenous glucose tolerance test (IVGTT) pre-operatively and repeated 1 month after islet transplantation

Table *The results expressed as median fasting values*

	Group 1	Group 2	Group 3	Group 4
Glucose (mmol/l)	5·5	5·5	7·0*	6·0
Insulin (milliunits/l)	18·9	15·3	22·4	12·5
Lactate: pyruvate	16·9	13·1*	16·9	16·4
Alanine (μmol/l)	425	444	446	387
Glycerol (μmol/l)	95	96	84	83
3-Hydroxybutyrate (μmol/l)	11·5	14·5	9·8	17·0
Free fatty acids (mmol/l)	0·43	0·53	0·26	0·47
Cholesterol (mmol/l)	5·16	6·40*	5·35	6·21

*See text below, all comparisons by Mann–Whitney *U* test

Compared with control animals, 1 month after transplantation group 2 dogs had a low lactate:pyruvate ratio ($P<0{\cdot}02$) and raised cholesterol ($P<0{\cdot}001$), while group 3 dogs were mildly hyperglycaemic ($P<0{\cdot}002$). In all transplanted groups, appropriate changes in intermediary metabolites and lipids occurred during IVGTT.

CsA does not adversely affect overall intermediary or lipid metabolism in islet autografted dogs and allows islet allografts to maintain metabolic normality. If, in clinical practice, islet graft survival could be maintained, metabolic normality would ensue and diabetic complications would be unlikely

Conservative adrenalectomy for bilateral phaeochromocytoma in patients with multiple endocrine syndrome Type II

R.C. Hickey and N.A. Samaan, *Departments of Surgery and Medicine (Endocrinology), University of Texas System Cancer Center, M.D. Anderson Hospital and Tumour Institute, Houston, Texas 77030, USA*

We report on eight patients with less than total bilateral adrenalectomy (six MEN IIA patients, one MEN IIB, and one with von Hippel syndrome). Cortical adrenal tissue was conserved *in situ*, and staged or delayed adrenalectomy was another alternative in MEN II patients. We also employed a combination of delay and then conservation; notably, in one MEN IIA patient this carried her through three uneventful pregnancies. We have been unable to do a free cortical transplant with proved function.

Follow-up without steroid replacement in the conservation resection has been for over three decades to a few months. In the conservation resection there is one questionable asymptomatic adrenal medullary recurrence, as detected by ^{131}I-labelled metaiodobenzylguanidine. Cortisol excretion data support the presence of functioning adrenal tissue following conservation.

The thrust of the study is to conserve functioning adrenal cortex to avoid potential Addisonian disease, particularly in the MEN II syndrome.

Operative treatment of nesidioblastosis

J.P. Murphy and R.C.G. Russell, *Department of Gastroenterology, The Middlesex Hospital, London, UK*

Nesidioblastosis is a rare abnormality of the pancreas causing persistent hyperinsulinaemic hypoglycaemia in young children. Delayed diagnosis and inadequate management results in repeated hypoglycaemic attacks Where adequate medical therapy fails to control the hypoglycaemia, surgical intervention is indicated. Previous reports suggested a conservative approach to resection, but the need for reoperation has been unacceptably high.

Nine children, from 1 week to 5 years old, have undergone a duodenal preserving, splenic preserving near total pancreatectomy, between 6 months and 6 years ago. At operation, the pancreas was normal in all but one patient who had a bulky body and tail of pancreas. A frozen section of the pancreas confirmed abnormal islet cell distribution in six, and subsequent histology including immunochemistry confirmed the diagnosis in all patients. More than 95 per cent of the pancreas was removed in six, 90 per cent in two and 80 per cent in the child with a bulky pancreas. There were no postoperative complications, and all children are still alive. Six children require no insulin; three children require insulin, two of whom also need enzyme supplements. One child required diazoxide, but is now off all treatment Growth appears normal.

It is concluded that near total pancreatectomy is an effective treatment for nesidioblastosis, and appears to have no adverse long-term sequelae.

Correspondence

Bowel preparation before sigmoidoscopy

Sir

We agree with Mann *et al* (*Br J Surg* 1988; **75**: 425–7) that preparation of the distal bowel, by means of disposable phosphate enema, is helpful before rigid sigmoidoscopy. However, when the facilities are available in the out-patient department to give enemas to patients requiring sigmoidoscopy the opportunity should be taken to examine the patient with a flexible, fibreoptic instrument whenever possible. A disposable enema will adequately prepare the bowel as far proximally as the splenic flexure in most cases and full insertion of a 65 cm flexible endoscope can be achieved in over 70 per cent[1] of cases Examination of at least 30 cm of bowel (the maximum distance achievable with a rigid instrument) is possible in almost all patients. In fact, Mann *et al* achieved passage of the rigid sigmoidoscope a mean distance of only 22·4 cm, despite bowel preparation and placing the patient in the unpopular knee-elbow position. Allowing for the apparent distance passed due to stretching of the rectum, this suggests that the rectosigmoid junction remains a difficult obstacle to negotiate with the rigid instrument.

However, the greatest argument for use of the flexible sigmoidoscope is that it will increase the number of occasions where cancer is diagnosed at a patient's first hospital attendance, simply owing to the extra length of bowel examined. In our experience, diagnosis of cancer at the initial consultation, without need for further investigation such as barium enema or colonoscopy, significantly reduces the delay between a general practitioner referring the patient and surgery. We suggest that any surgeon with the opportunity to give patients limited bowel preparation in the out-patient department would do better to invest in a flexible sigmoidoscope than a Ritter table.

J. J. T. Tate
G. T. Royle

University Surgical Unit
Southampton General Hospital
Southampton SO1 6HU
UK

1. Vellacott KD, Roe AM, Mortensen NJMcC. An evaluation of a direct access flexible fibreoptic sigmoidoscopy service. *Ann R Coll Surg Engl* 1987, **69**: 149–52.

Recurrent inguinal hernias

Sir

Mr Marsden (*Br J Surg* 1988; 75: 263–6) presents a most instructive review of carefully followed recurrent hernia repairs by different techniques. Support for the use of mesh by Mr Tinckler (*Br J Surg* 1988; 75 499) and abdominal placement of the testis (Mr Kirk, *Br J Surg* 1988; **75**: 499) add surgical ingenuity and improve on older techniques

Surely we must not neglect the Shouldice contribution to this subject? The fundamental principle of transversalis fascia division followed by overlapping repair has been standardized since 1951 Glassow[1] presents his personal series of recurrent inguinal hernias with 70 failures from 2609 repairs. Meshes were never used and the cord structures never deliberately divided—clearly they are endangered in multirecurrent cases so patients are warned of this. My own small prospectively reviewed series has 8 failures from 278 recurrent hernias using a modified Shouldice technique. As with all Shouldice disciples, we include later femoral hernias as recurrences. The aim of groin hernia repair must be to find and repair any type of hernia—indirect, direct or femoral—at the first operation Any further hernia is by definition a recurrence even if it does not require reoperation or a truss.

Perhaps someone should conduct a controlled trial of mesh repair *versus* Shouldice repair ± cord division? I am too biased by the success of the modified Shouldice type of repair to take part It is eminently suitable for all groin hernias, primary or recurrent Until this or a similarly successful repair is universally and correctly applied, we will all have too much experience of recurrent hernia repair.

N. J. Barwell

Royal Cornwall Hospital
Truro
UK

1. Glassow F. The Shouldice Hospital Technique. *Int Surg* 1986; **71**: 148–53.

Duodenal erosion complicating an implanted hepatic arterial catheter

Sir

There may be an alternative explanation besides pressure necrosis for the duodenal erosion complicating an implanted hepatic arterial silicone catheter as described by Cherqui *et al* (*Br J Surg* 1988; **75** 556) Giant duodenal ulcers have been described[1–3] in patients treated with hepatic artery chemotherapy for liver secondaries from the colon and breast (the latter also received radiotherapy) and for hepatomas The right gastric and gastroduodenal arteries were ligated. Goldin *et al* [2] described four patients who developed symptoms of pain or severe bleeding 5–7 months after the initial treatment, the two patients who bled died whereas the two with penetrating ulcers survived.

Suggestions for the cause of these ulcers have included duodenal ischaemia secondary to ligation of the right gastric and gastroduodenal arteries leading to mucosal damage. The infusion of drugs into the liver which are excreted through the hepatobiliary system may also produce local injury, and in some of these patients radiotherapy would also have contributed to tissue damage.

The patient described by Cherqui *et al.* probably represents another example of a giant duodenal ulcer with a local perforation as well as penetration. Endoscopy before and after such treatment has been advocated[2] to identify patients at risk from this problem The prophylactic use of H_2 antagonists or other 'anti-ulcer' drugs may have a role in preventing such serious complications

N. Heaton

The Dulwich Hospital
London SE22 8PT
UK

1. Crowley ML. Penetrating duodenal ulcer associated with an operatively implanted arterial chemotherapy infusion catheter *Gastroenterology* 1982; **83**: 118–20.
2. Goldin E, Peretz T, Libson E Giant duodenal ulcer. the hepatic intra-arterial variant *Postgrad Med J* 1988; **64** 431–3.
3. Wells JJ, Nostrant TT, Wilson JAP, Gyves JW Gastroduodenal ulcerations in patients receiving selective hepatic artery infusion chemotherapy. *Am J Gastroenterol* 1985, **80**: 425–9

Risk to surgeons

Sir

We read with great interest the paper of S. A. Hussain *et al.* 'Risk to surgeons: a survey of accidental injuries during operations' (*Br J Surg* 1988; **75**: 314–16). This paper addresses the important and topical issue of the risk surgeons are exposed to particularly from needle stick injuries. However, we feel that this large study may under-estimate the risk of glove puncture. The rate of accidental injuries quoted, 5·6 per cent, was based on injuries reported by the surgeons No account was taken of injuries of which the surgeon was unaware The published findings (*Table*) indicate that the surgeon is unaware of damage to his glove on from 46 to 61 per cent of occasions. This may account for the lower figure quoted by Hussain *et al.*, approximately half that of other series where all gloves were tested.

Authors	Punctures: surgeon not aware (%)	Gloves punctured (%)
Brough *et al.*[1]	61	19
Lafferty and Wyatt[2]	46	—
Matta *et al.*[3]	49	10·6
Church and Sanderson[4]	—	11·5

Thus with a glove perforation rate of at least one in ten gloves, surgeons may like to consider wearing two pairs ('double gloving') which substantially reduces the risk of a sharp instrument reaching the surgeon's skin[3] Even if the instrument does not actually penetrate the surgeon's integument, the risk of transmission of infected material through the resulting soaked skin may remain. Similarly, wearing a plastic apron or waterproof gown and spectacles or visor may also reduce the risk of contamination.

In the current climate, examining the risks to which surgeons are exposed and attention to surgical dress in addition to surgical technique may be to the advantage of all concerned

H. Matta
A. M. Thompson

The Royal Infirmary
Edinburgh EH3 9YW
UK

1. Brough SJ, Hunt TM, Barrie WW. Surgical glove perforations *Br J Surg* 1988, **75**: 317.
2. Lafferty K, Wyatt AP After safe surgery, safe sex. *Br Med J* 1987; **295**: 392 (letter)
3. Matta H, Thompson AM, Rainey JB. Does double gloving protect? *Br Med J* 1988; **297** (in press).
4. Church J, Sanderson P. Surgical glove punctures. *J Hosp Infect* 1980; **1**: 84 (letter).

Thyroglossal duct cyst recurrence

Sir

It was with interest that we read the paper by Tetteroo *et al* (*Br J Surg* 1988; **75**: 382–3). Their study reiterates the knowledge gathered over many years concerning the surgical management of thyroglossal duct remnants and their potential to recur[1,2].

We agree that total excision of thyroglossal duct epithelium is necessary in order to reduce the possibility of recurrence but find it curious that so much emphasis is placed only upon excising the tract upwards to the hyoid bone and tongue. Indeed this is obviously important but what of the remnants that pass down to the thyroid isthmus? Sistrunk[3] in his original treatise does not describe an inferior dissection as part of his technique and this omission may give rise to cases of recurrence

To this end, a recent case presented with a recurrence of a thyroglossal duct cyst, 18 years after four previous attempts at its removal. The middle third of the hyoid bone had been excised at the last operation. On exploring the region this time, an infected thyroglossal remnant situated just superior to the thyroid cartilage was excised. Excision also included a tract which passed down to the thyroid isthmus and histological examination confirmed that it was of thyroglossal origin. Recurrence in this case seems to be because no previous attempt had been made to remove remnant tissue between the original cyst and the thyroid gland.

We conclude therefore that if thyroglossal remnants are to be completely excised, it is not sufficient just to remove the middle third of the hyoid bone but the inferior dissection must begin immediately superior to the thyroid isthmus. This approach has been described as a modified Sistrunk procedure[4] and is especially advocated in cases of recurrence.

S. N. Rogers
M. A. Feldman

Dudley Road Hospital
Birmingham B18 7QH
UK

1. Ein SH, Shandling B, Stephens CA, Mancer K The problem of recurrent thyroglossal duct remnants *J Ped Surg* 1984, **19**: 437–9
2. Bennett KG, Organ CH, Williams GR Is the treatment for thyroglossal duct cysts too extensive? *Am J Surg* 1986; **152**: 602–5.
3. Sistrunk WE. The surgical treatment of cysts of the thyroglossal tract *Ann Surg* 1920; **71**: 121–4.
4. Mickel RA, Calcaterra TC. Management of recurrent thyroglossal duct cysts *Arch Otolaryngol* 1983, **109**: 34–6.

T tubes: virgin, slit, guttered or sculpted

Sir,

In the SRS abstracts (*Br J Surg* 1988; **75**: 615) it is suggested that a sculpted T tube is likely to be important in preventing the complication of bile peritonitis after T tube removal.

On 6 April 1988 I carried out a cholecystectomy and exploration of the common bile duct on a 65-year-old woman. Two stones were retrieved from the common duct and a sculpted T tube was inserted. She had a mild micronodular cirrhosis but no significant portal hypertension; the operation was uneventful.

The postoperative cholangiogram was normal and the T tube was removed on the tenth postoperative day The nurse removing the tube remarked how easily it came out. Within 20 min of its removal the patient had agonizing abdominal pain which was referred to the right shoulder. There were signs of spreading peritonitis and she was re-explored. There was a large amount of bile in the peritoneal cavity. The T tube was re-inserted. Following the second operation she made a satisfactory recovery and the T tube was removed without incident 6 weeks later.

It seems likely that the problem of bile peritonitis following removal of a T tube is more likely to be related to the 'walling off' of the tube track than the shape of the T tube used

J. L. Dawson

King's College Hospital
London SE5 9RS
UK

Pancreatitis and hyperparathyroidism

Sir,

I should like to comment on the interesting article on 'Pancreatitis and hyperparathyroidism' by Sitges-Serra *et al.* (*Br J Surg* 1988; **75**: 158–160)

It is not correct to state that the first case report of such a condition was by Martin and Canseco in 1947. In 1940, Smith and Cooke[1] described a patient who died of 'acute poisoning by parathyroid hormone' and, at necropsy, found a parathyroid adenoma associated with acute necrosis of the pancreas. There are even earlier reports of acute fatal hyperparathyroidism where the authors[2–4] described widespread calcium salt deposits in various internal organs of the body although no specific mention of the pancreas was made. It has also been shown[5,6] that calcification in the substance of the pancreas is invariably intraductal in origin. This is also my experience in the few cases I have examined. Renal calculi are well recognized. Salivary calculi have also been reported[7]

That pancreatitis is a complication cannot be denied. However, the incidence of pancreatitis in hyperparathyroidism can be expected to go on decreasing, provided steps are taken for early diagnosis and treatment This explains the low incidence of pancreatitis in the series of Bess *et al.*[8] (1·5 per cent reported in 1980) compared with 4 per cent in the report of Hellstrom[9] in 1954, 7 per cent by Mixter[10] in 1962, and 2·9 per cent by Herskovic *et al.* in 1967[11]. It is also very interesting to mention Jackson's series[12] of hereditary hyperparathyroidism where a woman, her two sons and three brothers were all found to have hyperparathyroidism and the first three of these gave a history of recurrent pancreatitis.

S. Jawaheer

Victoria Hospital
Quatre Bornes
Mauritius

1. Smith FB, Cooke RT. Acute fatal hyperparathyroidism *Lancet* 1940; **ii**: 650–1.
2. Dawson JW, Struthers JW. Generalized osteitis fibrosa, with parathyroid tumour and metastatic calcification, including critical discussion of pathological processes underlying osseous dystrophies. *Edin Med J* 1923; **30**. 421–565.
3. Hanes FM. Hyperparathyroidism due to parathyroid adenoma with death due to parathormone intoxication. *Am J Med Sci* 1939; **197**: 85–90.
4. Oliver WA. Acute hyperparathyroidism. *Lancet* 1939; **ii**. 240–44.
5. Coffey RF, Canary JJ, Dermais CC. Hyperparathyroidism and chronic calcific pancreatitis. *Am Surg* 1959, **25**: 310–13
6. Owen JL, Howard JM. Pancreatic calcification: a late sequel in the natural history of chronic alcoholism and alcoholic pancreatitis. *Ann Surg* 1958, **147**: 326–38.
7. Stanbury SW. Quoted by Jawaheer S. *Br Med J* 1963, **1**: 450–1.
8. Bess MA, Edis AJ, Van Heerden JA Hyperparathyroidism and pancreatitis: chance or a causal association? *JAMA* 1980; **243**: 246–7.
9. Hellstrom J. Primary hyperparathyroidism: observations in a series of 50 cases. *Acta Endocrinol* 1954, **16**. 30–8.
10. Mixter CG, Keynes WM, Cope O Further experience with pancreatitis as a diagnostic due to hyperparathyroidism. *N Engl J Med* 1962; **266**: 265–71.
11. Herskovic T, Keating FR, Gross JB Coexisting pancreatitis and hyperparathyroidism. *Gastroenterology* 1967; **52**: 1093.
12. Jackson CE. Hereditary hyperparathyroidism associated with recurrent pancreatitis. *Ann Intern Med* 1958, **49**: 829–36.

Book reviews

Cost-effective Surgical Management

B. Eiseman and L. Stahlgren. 265 × 180 mm. Pp. 314 + xxi. Illustrated. 1987 Philadelphia W. B. Saunders £35.75

This book is much more than its title suggests. It is a wide ranging multi-author review of sensible surgical practice with cost (to the patient and not to the institution) as a unifying theme. Once the reader has found his way through the American surgical terminology and billing practice, he will find a book in five distinct sections.

The first section discusses the general considerations of cost-effectiveness. It contains one of the most lucid discussions of test effectiveness, sensitivity and specificity that the reviewer has read. This leads into a discussion of the merits of a wide range of surgical managements. Particularly thought provoking is the section on the costs to patients of hospital treatment away from home The second section considers cost-effective diagnosis, the third treatment and the fourth some individual operations. The final section is a summary of what has gone before, written in a pithy and concise style by the editors. Throughout the book the individual authors keep to a general format which gives cohesion It is encouraging to find the general conclusions that good surgery is cost-effective, that good investigation is selective and that Osler's holistic view of medicine is economically viable.

This is an immensely detailed book which your reviewer found challenging and rewarding to read. British surgeons will find that it crosses the Atlantic well and that they will learn both surgical and economic truths within it.

I. G. Kidson

Whittington Hospital
London N19
UK

Emergency Abdominal Surgery

P F. Jones 192 × 252 mm. Pp. 499. Illustrated. 1987 Oxford· Blackwell Scientific £49 50

Specialization in surgery has led to the almost total disappearance of single author textbooks Surgery of the acute abdomen, although demanding a broad knowledge and wide range of surgical skills, remains the general surgeon's speciality and as such is ideally suited to be covered by one author In *Emergency Abdominal Surgery* the author has combined his immense experience in the field with obvious enthusiasm for the subject to produce a work of great authority, thoughtfully constructed and consistent in style which was a pleasure to read. With outstanding success he has achieved his aim of combining a review of the subject and its literature with a handbook for the surgical trainee

The book starts with an excellent introduction emphasizing the importance of the clinical skills of history taking, observation and careful eliciting of physical signs, a point stressed repeatedly throughout the book The whole subject is well covered and the chapters on abdominal emergencies in infancy and childhood, intestinal obstruction, large bowel emergencies and peritonitis are particularly good. Throughout the book, reference is made to the author's documented experience; he quotes many of his own series and those of his hospital colleagues to support his recommendations on management and technique. The bibliography is extensive and up to date The references follow each section which is very helpful in the longer chapters. The book contains relatively few illustrations· they are in the form of simple line drawings which are clear and illustrate specific points in the text.

The basic principles advocated throughout the book are sound and safe. One would not expect every surgeon to agree with all the author's views and techniques, but a trainee surgeon following the principles and practices advocated would not go wrong The book is an ideal supplement to a practical, supervised surgical training I strongly recommend it to all surgical trainees learning the skills of emergency abdominal surgery and preparing for the final Fellowship.

J. Bolton

Consultant Surgeon
Chase Farm Hospital
Middlesex
UK

Principles of Gynaecological Surgery

S. L Stanton. 275 × 200 mm. Pp. 306 + xii Illustrated 1987 New York. Springer Verlag. £29.50.

One of the major failings of nearly all training programmes in gynaecology is the absence of any formalized teaching in general surgery and, most especially, in the general principles of surgery The publication of a book that is concerned solely with these general principles but which also is directed at the gynaecologist is a most welcome addition to the gynaecological literature This book is divided into three main sections which cover pre-operative, operative and postoperative problems. In the first section, the pre-operative preparation of the patient is discussed, to include consent and its validity and with a special section on the pre-operative management of the elderly Included in the first section are also excellent reviews on the prevention of treatment of thrombo-embolism and of surgical sepsis, together with good chapters on the recent advances in diagnostic imaging and in anaesthesia.

In the operative section there is a superb chapter on operative positions, incisions and closure although the absence of any mention of incisions in relation at least to the first half of pregnancy was a sad omission as this latter situation is frequently faced by the gynaecologist. Further chapters on the management of peroperative intestinal and urological damage and also of haemorrhage are included, together with an excellent chapter on recent developments in suture materials In this section are also very comprehensive chapters on gynaecological microsurgery and the use of the laser. The last section covers postoperative problems such as intensive care, resuscitation, and also a review of the metabolic responses to surgery Further chapters on the management of urological and intestinal injury are very useful. The section is concluded with a review of the psychiatric sequelae of gynaecological surgery.

A book of this standard which covers the principles of gynaecological surgery in such a systematic and helpful way is long overdue, and Stuart Stanton must be congratulated for putting together such an excellent publication I was also delighted to see the dedication of this book to John Dickinson whose teaching was an inspiration to us all This book should be required reading for all those entering the specialty of gynaecology and I would thoroughly recommend that it is included in all medical libraries.

A. M. Jequier

Senior Lecturer in Obstetrics and Gynaecology
Nottingham
UK

Practical Burns Management

H Kemble and B. E Lamb. 138 × 215 mm. Pp. 208. Illustrated. 1987. London Edward Arnold. £9.95.

In the opening chapter of this worthy paperback, the authors state that 'Fire has savaged man's ancestors since he appeared on Earth' Over the last 2 years there have been countless major and minor fire accidents ranging from the flash fire at King's Cross, to smoke inhalation fires from foam rubber sofas, and the horrors at Chernobyl. This book is, therefore, a timely up-to-date review of burns management.

It is indeed a practical work which will appeal to casualty officers and surgical senior house officers, registrars, staff nurses and sisters when faced with a burn injury. There are extensive tables, conversions and examples of how to calculate the extent of injury and the volume of fluid replacement. Each section is well laid out, has excellent summaries and presents a balanced view Not only is the specific management detailed for chemical, electrical and radiation injuries but, in addition, the psychological needs of the patient are stressed

Armed with this book, the district hospital team will do well However, I do feel that at £9.95 the publishers are trying to burn an unnecessary hole in our pocket!

M. Kissin

Senior Registrar in Surgery
Bristol Royal Infirmary
Bristol
UK

Small-bowel Transplantation

E. Deltz, A Thiede and H. Hamelmann. 168 × 247 mm. P 257. Illustrated 1987. New York: Springer Verlag. DM180.00

Progress in small bowel transplantation has failed to keep pace with that achieved in recent years with other organs. The increasing numbers of patients surviving on home total parenteral nutrition and the advent of cyclosporin has caused renewed interest in small bowel grafting.

This short book reports the deliberations of a workshop held in Kiel, FRG, in October 1985 and brings together investigators in the field from western Europe and North America. Because experience of small bowel transplantation in humans has been very restricted and disappointing, the scientific content is confined to work in small and large animals. The first section deals with the advantages of using inbred strains of rats to achieve a stable transplant model. Sections 2–5 describe the technical and immunological problems in achieving survival in large animals. At present the impact of cyclosporin is variable and disappointing, and is achieved only with toxic doses of the drug Sections 6–10 assess the projected needs and logistical problems in clinical transplantation The estimated need is two cases per year in the UK and 58 per year in the USA. In France plans are being developed for small bowel transplantation in children

For the first time the results of all the groups of workers in this field have been compiled in one volume. Although of limited interest to general surgeons, it is an essential source of information and references for those interested in this important subject.

S. T. D. McKelvey

Consultant Surgeon
The Ulster Hospital
Belfast
UK

Acute Medical Problems in the Postoperative Patient

G. A. Porter. 160 × 233 mm. Pp 216. Illustrated 1987. Edinburgh Churchill Livingstone. £19.95.

This is a book dedicated to house surgeons and surgical registrars grappling with the difficult postoperative patient. It is written in an easily understandable style, it covers all the common medical emergencies to be found on a surgical ward and it is set out in a fashion that must become standard reference text for junior surgical staff

Surgical audit indicates that not only is the selection of patients for surgery at fault but also the surgeons' management of concurrent medical problems is to be criticized. This book begins to correct both of these deficiencies in that it covers in detail the major respiratory, cardiovascular and renal problems that are so often the cause for the demise of otherwise straightforward surgical patients. The book is edited by a physician who has a long experience of teaching students and he has drawn widely on his physician colleagues in Oregon Data are often reduced to tables and figures to make it easily digestible and, although traditional organ system classification is mainly followed, presentations that are more systemic in nature are dealt with in separate sections.

Appropriately, large sections of the book are dedicated to cardiovascular and respiratory problems, especially management of arrythmias and the assessment of patients for surgery following myocardial infarction. At the end of each chapter there is a suggested reading list so that further study can be undertaken. Subjects are dealt with in such a way that the junior surgical team would be reassured that an appropriate management procedure is being performed.

Closer reading of the chapter concerned with renal problems shows some defects Whereas the infective aspects of the causes of renal failure are not excluded, there is very little space given to this important subject. Some discussion on the localization of sepsis and its non-interventional and operative management would be appropriate in a book of this size In the discussion of deep venous thrombosis, the emphasis is inevitably on the management of postoperative thrombo-embolism with very little discussion on the prophylaxis. The prophylaxis that is mentioned is purely chemical with no mention of the mechanical methods

Overall this is an excellent book, well written and suitable for medical students and junior staff

J. A. Rennie

Senior Lecturer in Surgery
King's College Hospital
London
UK

Platelet–Vessel Wall Interactions

R. M. Pittilo. 168 × 248 mm. Pp. 187. Illustrated 1988. New York Springer Verlag. £47 00.

This compact monograph is the second in the Bloomsbury series in clinical science, and comes from the Middlesex Hospital and the Institute of Urology. The underlying theme of the book is the pathophysiology of atherosclerosis and, in particular, the relationship between disturbance of platelet–endothelial function and vessel disease The introductory chapters provide an in-depth account of the platelet and vascular endothelium, and describe methods of culture of vascular endothelial cells, and how these cells are employed in studying growth factors and the effects of toxic substances such as nicotine The effects of smoking on the platelet and vessel wall are analysed in detail. We are then provided with a fascinating account of the use of cultured mesothelial cells to provide a non-thrombogenic surface on prosthetic vascular grafts, and how these cells are affected by cigarette smoke.

Attention then turns to the possible role of the platelet in renal injury, and the various disturbances of platelet function which may be seen in renal disorders. This is followed by an account of the haemolytic uraemic syndrome and thrombotic thrombocytopaenic purpura The book concludes with a review of the newer pharmacological agents influencing platelet–vessel wall interactions and, in particular, their mode of action and theoretical value The drugs considered include those affecting prostaglandin metabolism, calcium channel blockers, factors affecting cyclic-AMP, and serotonin antagonists.

This book, with its excellent illustrations and prolific references, will be of considerable interest to basic and clinical scientists working in the fields of vascular disease and thrombosis.

B. Pardy

Consultant Surgeon
Newham General Hospital
London E13 8SL
UK

Lithotripsy II

M. J. Coptcoat, R A. Miller and J. E A Wickham. 158 × 240 mm Pp. 195. Illustrated. 1987. London· B.D I. Publishing, £35 00.

Surgeons may be surprised that the reviewer is a radiologist. Lithotripsy is, however, starting to cross boundaries—emerging from the renal tract (where it started in the kidney and now includes the ureter) and exploring the biliary system. The essence of successful lithotripsy is the application of the small shock wave focus to the calculus using a variety of imaging systems and a considerable knowledge of three-dimensional anatomy. Perhaps an imaging specialist crossing the boundaries between urology and gastro-enterology can best provide this service leaving the clinical management and over-view to the specialist surgeon.

The book is in two sections plus an introduction. The opening chapter which most surgeons will find stimulating and provocative is followed by a chapter devoted to basic principles and physics.

The first section is a series of presentations by various manufacturers. These are somewhat partisan extolling the virtues and effectiveness of their equipment, hinting at their limitations by omission rather than commission

The second part is a collection of chapters on ancilliary techniques, mainly associated with the urinary tract, without which lithotripsy would not be viable. It cannot be a definitive text on lithotripsy but it is an excellent monograph on the current state of the art, it will be many years in advance of a definitive text owing to the rapid technical progress of lithotripsy in all its aspects. The book provides fascinating glimpses of third generation lithotripters and beyond as the search continues for cheaper, less painful and more user friendly apparatus. It is salutary to realize how far Britain has been left behind in this field.

Although the book is primarily aimed at urologists, most clinicians involved in the management of renal and biliary calculi will find this a stimulating work. It illustrates how interdependent are the many branches of medicine and science in these new developments. It should find a place in most acute hospital libraries and is essential reading for those involved, either actively or by referral, in lithotripsy

B. Ross

Consultant Radiologist
Sheffield
UK

Gastroenterologic Endoscopy

M. V. Sivak. 190 × 262 mm. Pp. 1168. Illustrated. 1987. London. Academic Press. £95 00.

This is a lengthy multi-author book covering all aspects of gastrointestinal endoscopy including laparoscopy. Although inevitably of variable quality and at time repetitious or out of date, the book succeeds in its main aim of providing a useful reference text.

The book has 1168 pages (although 24 were missing from my copy), 75 authors and 57 chapters. Two-thirds of the authors are based in North America, the remainder coming equally from Europe and Japan. The initial section covers the history of gastrointestinal endoscopy, the basic technology of fibreoptic endoscopy and interventional methods, and the organization and administration of an endoscopy service. This is followed by sections on the techniques, results and complications of upper gastrointestinal endoscopy, ERCP, colonoscopy and laparoscopy. The book has an old-fashioned 'feel', probably because of its format and the style of the figures and illustrations which are of very variable quality and value. There is considerable repetition and overlap in separate chapters, and at times the authors have strayed from endoscopy into more general aspects of gastro-enterology. The rapid changes in endoscopic technology and the results of recent studies mean that in some areas the text is already out-dated. Despite these criticisms, this book should prove a useful and comprehensive reference text, providing much detailed information collected during the first 20 years of fibreoptic gastrointestinal endoscopy.

J. N. Thompson

Lecturer in Surgery
St. Mary's Hospital
London
UK

1987 Year Book of Digestive Diseases

N. J. Greenberger 155 × 234 mm. Pp. 462. Illustrated. 1987. London. Wolfe Medical Publications. £37 50.

I must confess that I have not previously picked up a copy of the *Year Book of Digestive Diseases*. Having read this one I don't think that I will rush for the next edition.

It is not that it is a bad book It is, in fact, quite good. The editors have chosen approximately 250 papers from a total of about 20 000 in 50 major journals. A useful synopsis of each paper is given. These are longer than a simple abstract and quite a number have a table or an illustration as well. Helpful personal comments have been added to most of the synopses which try to put things into perspective. Inevitably one can disagree with personal selection and the associated comments. In general I thought that the editors had chosen well and I appreciated most of the comments. The book is also well indexed which makes it easy to use.

The trouble is that gastro-enterology is now well served by some excellent abstracting services. I receive two free of charge and find these an invaluable aid to systematic reading. It is quite impossible to produce a fully bound book as quickly and economically as something in journal format. The producers of the Year Book series therefore start at a considerable disadvantage and I don't think they can beat my 'freebies' even if the latter are less polished productions.

J. Bancewicz

Senior Lecturer in Surgery
Hope Hospital
Manchester
UK

Diagnostic Picture Tests in General Surgery

W. Walker. 184 × 188 mm. Pp. 200. Illustrated 1987 London Wolfe Medical Publications. £6 50

This small handbook is a self-assessment manual, involving diagnostic picture tests of situations arising within the full scope of general surgery. It is very carefully prepared and well illustrated and will be found useful particularly by candidates preparing for the Fellowship examinations. The illustrations consist of photographs of physical signs or operative findings, together with a variety of radiological problems. In all, 200 different clinical problems are shown with the answers in a separate section at the back of the book Both the questions and answers are simple and to the point. This book is a useful adjunct to any candidate preparing for a surgical examination, or even perhaps as a refresher for the examiners themselves.

P. D. Wright

Consultant Surgeon
University of Newcastle
Newcastle
UK

Erratum

'Choledochocele. treatment by endoscopic sphincterotomy' by J. J. Gerritsen, A. R. Janssens and H. M. Kroon, *Br J Surg* 1988; 75: 495–496, page 495, line 17, after 'Intravenous cholangiography was normal.' the following section was omitted: 'In 1972 further evaluation showed a right hydroureter and hydronephrosis and a duplication of the left renal pelvis and ureter. The right ureter was re-implanted into the bladder. However the attacks of pain persisted. In 1974 a right-sided nephrectomy was performed because of far advanced chronic pyelonephritis and in 1976 the ureter from the higher part of the left kidney was connected to the pelvis of the lower part. Neither operation relieved her symptoms ' We apologize for this error.

Notices and announcements

18–23 September 1988
The Second Oxbridge Organ Transplantation Course
Cambridge, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1988
Oxford Postgraduate Seminar on Early Intervention in Major Trauma
Oxford, UK
Information: Dr P. Nash, Casualty Surgeons Association, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–30 September 1988
Royal Microscopical Society Ultrastructural Anatomy Course
Belfast, UK
Information: The Administrator, Royal Microscopal Society, 37/38 St Clements, Oxford OX4 1AJ, UK

29–30 September 1988
Heparin and Related Polysaccharides
London, UK
Information: Penny Robinson, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EX1A 2EX, UK

29–30 September 1988
Access 88: Current Techniques of Access for Dialysis, Nutrition and Cancer Therapy
Leicester, UK
Information. Mr P. K. Donnelly, Department of Surgery, The General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

30 September 1988
9th Annual Study Day: the Role of the Plain Abdominal X-ray in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

5–8 October 1988
4th Congress of the European Society of Surgical Oncology (ESSO 88)
Paris, France
Information ESSO 88, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France

5–8 October 1988
4 Jahrestagung Der Deutschen Gesellschaft Für Lasermedizin
Vienna, Austria
Information. Doz. Dr A Tuchmann, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Vienna, Austria

20 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information. Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

24–27 October 1988
American College of Surgeons Meeting: 74th Clinical Congress
Chicago, USA
Information Fred C. Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

26 October 1988
British Society for Surgery of the Hand. Basic course: Care of Hand Injuries. Advanced course: Reconstructive Surgery after Trauma
London, UK
Information Honorary Secretary of BSSH at the Royal College of Surgeons, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

30 October–1 November 1988
13th Congress of the European Society for Medical Oncology (ESMO)
Lugano, Switzerland
Information Dr F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

30 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

4–7 November 1988
Integrated Management of Head and Neck Cancer
Grantham, UK
Information Mr P. J. Bradley, Consultant ENT Surgeon/Head and Neck Oncologist, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK

17–19 November 1988
Eighth Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information Mrs Marty May, Secretary to LTC Warren, F. Bowland MD, Chief, Trauma Service, Department of Surgery, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

25–26 November 1988
European Symposium on Ultrasonic Radiation Safety
Copenhagen, Denmark
Information Mrs A G Thorn, Ultrasound Laboratory, Glostrup Hospital, DK 2600 Glostrup, Denmark

25–27 November 1988
22nd Annual Combined Surgical Meeting
Singapore
Information. The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

28 November–2 December, 1988
Symposium and Workshop on Vascular Surgery
Singapore
Information. The Secretariat, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0306

8th December 1988
British Association of Surgical Oncology Forum: 'Head and Neck Cancer for the General Surgeon'
London, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

9 December 1988
Angioplasty: a Surgical or Radiological Procedure
London, UK
Information Janet Williamson, Secretary to Frank Ellis, 5 New Guy's House, Guy's Tower, London SE1 9RT, UK

9–10 December 1988
British Association of Surgical Oncology Forum: Winter Meeting
London, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–18 December 1988
Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons
Las Vegas, USA
Information: Dr M. R. Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988
Association of Surgeons of India Golden Jubilee Annual Conference
New Delhi, India
Information. Dr N. C. Madan, Organizing Secretary 'ASICON-88', Room No 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information. Congress Secretariat, 7th Congress Asian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

The American Journal of Surgery

AUGUST 1988/VOLUME 156/NUMBER 2

Contents

Papers of the Society for Clinical Vascular Surgery

PRESIDENTIAL ADDRESS

80 **Assessing Success**
Joseph G. Sladen

SCIENTIFIC PAPERS

83 **A New Quantitative Spectrophotometric Assay of Ischemia-Reperfusion Injury in Skeletal Muscle**
Michael Belkin, Richard D. Brown, J. Gordon Wright, Wayne W. LaMorte, and Robert W. Hobson II

87 **Does Intracranial Dye Study Contribute to Evaluation of Carotid Artery Disease?**
Donald L. Akers, William H. Bell, and Morris D. Kerstein

91 **Is Duplex Follow-Up Cost-Effective in the First Postoperative Year After Carotid Endarterectomy?**
Mark A. Mattos, Asad R. Shamma, Nicholas Rossi, Ronald Meng, John Godersky, Christopher Loftus, and John D. Corson

96 **Analysis of 18 Recent Cases of Penetrating Injuries to the Common and Internal Carotid Arteries**
Joseph P. Meyer, James Walsh, John Barrett, James J. Schuler, Joseph R. Durham, Jens Eldrup-Jorgensen, Thomas H. Schwarcz, and D. Preston Flanigan

100 **Aortobrachiocephalic Reconstruction**
William E. Evans, Thomas E. Williams, and James P. Hayes

103 **Cardiac Risk Index as a Predictor of Long-Term Survival After Repair of Abdominal Aortic Aneurysm**
Geoffrey H. White, Suresh M. Advani, Russell A. Williams, and Samuel E. Wilson

108 **Selective Use of Retroperitoneal Aortic Exposure in the Emergency Treatment of Ruptured and Symptomatic Abdominal Aortic Aneurysms**
Benjamin B. Chang, Philip K. Paty, Dhiraj M. Shah, and Robert P. Leather

111 Experimental Prosthetic Vein Valve
Syde A. Taheri, David Rigan, Philip Wels, Robert Mentzer, and Robert M. Shores

115 **Neurovascular Injuries of the Thoracic Outlet and Axilla**
Stanley R. Klein, Frederic S. Bongard, and Rodney A. White

119 **Tube Graft Replacement of Abdominal Aortic Aneurysm**
William E. Evans and James P. Hayes

122 **Origin of Deep Vein Thrombi in an Ambulatory Population**
David L. Rollins, Carolyn M. Semrow, Mark L. Friedell, William E. Lloyd, and Dale Buchbinder

126 **The Demise of Primary Profundaplasty**
Timothy R.S. Harward, John J. Bergan, James S.T. Yao, William R. Flinn, and Walter J. McCarthy

130 **Analysis Of Urokinase Immobilization on the Polytetrafluoroethylene Vascular Prosthesis**
Robert I. Forster and Fred Bernath

133 **Durability of the Tibial Artery Bypass in Diabetic Patients**
Dhiraj M. Shah, Benjamin Chang, Kathleen M. Fitzgerald, Jeffrey L. Kaufman, and Robert P. Leather

136 **Popliteal Artery Injury Complicating Arthroscopic Menisectomy**
Roy L. Tawes, Jr., Stephen N. Etheredge, Ronald L. Webb, Leslie J. Enloe, and Robert J. Stallone

139 **Midgraft Curettage as a Routine Adjunct to Salvage Operations for Thrombosed Polytetrafluoroethylene Hemodialysis Access Grafts**
John W. Puckett and Stephen F. Lindsay

143 **Do Operative Results Justify Tibial Artery Reconstruction in the Presence of Pedal Sepsis?**
Jeffrey R. Rubin, Howard C. Pitluk, and Linda M. Graham

148 **Correlation of Clinical Findings With Venous Hemodynamics in 386 Patients With Chronic Venous Insufficiency**
C. Scott McEnroe, Thomas F. O'Donnell, Jr., and William C. Mackey

A12 ***The British Journal of Surgery* Table of Contents (vol. 75, no. 8, August 1988)**

CORRECTION

In the article entitled "Adenocarcinoma of the Appendix," which appeared in the March 1988 issue (155: 470-475), the byline was not complete. The Association Universitaire de Recherche en Chirurgie should have been credited for authorship in addition to Lenriot JP and Huguier M because the study was the result of a joint effort of that group. The Editor apologizes to Drs. Lenriot and Huguier and reiterates that their designation as sole authors was erroneous.

PERCUTANEOUS GALL BLADDER SURGERY AND RADIOLOGY

THE NEW ONE-STAGE TECHNIQUE

Monday, 17 October 1988

London, England

BDI
conferences

WELCOME . . .

A new one-stage technique to remove gall stones percutaneously has been developed from experience with percutaneous nephrolithotomy This **INTENSIVE ONE DAY COURSE** will summarise recent endoscopic and radiological developments with **LIVE** closed circuit **TELEVISION DEMONSTRATIONS** of percutaneous endoscopic gall stone extraction.

MEETING STRUCTURE

Lectures – Live television demonstrations – Panel discussions – Trade exhibition

ORGANISING COMMITTEE

C Hudd FRCS
M J Kellett MA FRCR
R C G Russell MS FRCS
J E A Wickham MS FRCS

SPEAKERS TO INCLUDE

R Mason FRCS DMRD
C Mallinson FRCP
W Lees MD FRCR
E Van Sonnenberg MD
and Members of the Organising Committee

GENERAL INFORMATION

VENUE

The Kensington Close Hotel, Wrights Lane, London W8 5SP, England
Telephone· 01-937 8121

TRAVEL AND ACCOMMODATION

A limited number of rooms have been reserved at *The Kensington Close Hotel*. If you are interested in these or wish to have details on special air fares please complete the appropriate section on the registration form

MIXING MEDICINE WITH DINNER AT THE SCIENCE MUSEUM

We have arranged a delightful reception to take place shortly after the course ends on the evening of October 17th We shall be dining at the famous Science Museum which has one of the finest and most unusual medical collections in the world and is situated within walking distance of the Kensington Close Hotel

METHOD OF PAYMENT

Cheques in sterling drawn on an English bank and made payable to *BDI Conferences Ltd* or by credit card We accept Access, Visa and American Express cards.

CANCELLATION REMITTANCES

Before September 17th – 70%
After September 18th – 25%

SECRETARIAT

Pauline Sleight, *BDI Conferences Ltd.*, 9-11 Kensington High Street,
London W8 5NP, England
Telephone. 01-938 2151
Telex 268828

Please return this form to
BDI Conferences Ltd, 9-11 Kensington High Street,
London W8 5NP, England

REGISTRATION FORM

PERCUTANEOUS GALL BLADDER SURGERY AND RADIOLOGY

Name Prof/Dr/Mr/Mrs____________

Full mailing address____________

____

____

Telephone____________

Registration fee (excl VAT) **£118.20** ________

+ VAT at 15% **£17.80** ________

Evening Social Programme 17th October

I shall be attending the buffet supper at The Science Museum (7 00pm) **£15 per person*** ☐ ________

Total payable________

I enclose a cheque* ☐ ________

PAYMENT BY CREDIT CARD

Access ☐ Visa ☐ American Express ☐

Credit Card Number

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry date____________

Name of cardholder____________

I authorise *BDI Conferences Ltd* to charge my Access/Visa/American Express card

Signature____________

ACCOMMODATION AND TRAVEL ARRANGEMENTS

Please send me details of accommodation at The Kensington Close Hotel* ☐

Please send me details of/organise my travel arrangements to and from London* ☐

My requirements are as follows *(please specify)*

____

____

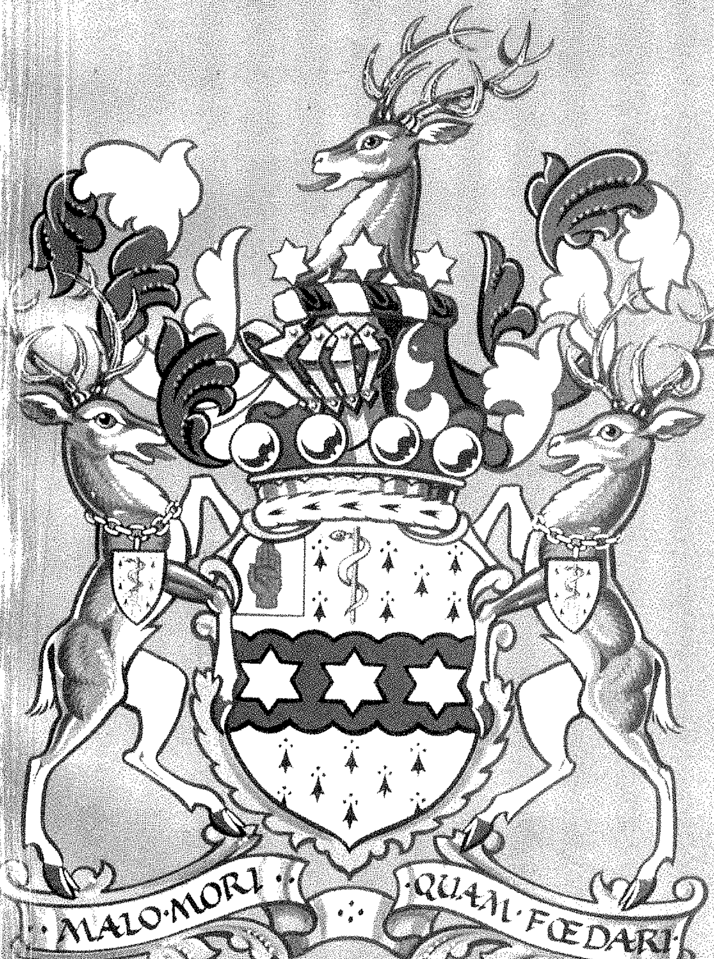
**Please tick boxes as appropriate*

THERE ARE ONLY A VERY LIMITED NUMBER OF PLACES ON THIS COURSE SO PLEASE REGISTER IMMEDIATELY

The British Journal of Surgery

ume 75, Number 10, October 1988

15.11.88



NOW AVAILABLE

20th Edition

BAILEY & LOVE'S SHORT PRACTICE OF SURGERY

Revised by
A.J. HARDING RAINS, CBE, MS, FRCS
and
CHARLES V. MANN, MCh, FRCS
with 36 specialist contributors

1355 illustrations (236 coloured), xii + 1406pp £35.00 net

H.K. LEWIS & CO. LTD

136 Gower Street, London WC1E 6BS
Telephone 01-387 4282 Telex 22607

Mawson's Diseases of the Ear

Fifth Edition

Edited by HAROLD H LUDMAN, Consultant Surgeon, Department of Otolarygology, King's College Hospital, London

The fifth updated edition of *Mawson's Diseases of the Ear* provides **in one volume** all the otological information necessary for those taking their final FRCS, for ENT consultants, physicians and general practitioners with an audiological interest.

"*. . . an excellent textbook and any candidate with a good grasp of its contents enters the fellowship examination well prepared in the field of otology.*" **Clinical Otolaryngology** (of the fourth edition)

Publication October 1988 £75 net boards 688 pages
ISBN 0 7131 4580 3 306 figures (line, half-tones and x-rays)

Plastic Surgery in Paediatrics

IAN L MUIR

(A Lloyd-Luke Publication)

Publication December 1987 £49.50 net boards 208 pages
ISBN 0 8532 42054 211 figures (line and half-tones)

Edward Arnold

A division of Hodder & Stoughton

41 Bedford Square, London WC1B 3DQ
Telephone: 01-637 7161

REPRINTS

Reprints of all articles in this journal are available in quantities of 100 or more.

Reprints are essential —

- for the company that wants to distribute impartial comment on its activities to potential customers and clients
- for the company that wants to up-date its technical staff on new techniques and new technologies

For full details of prices and availability of reprints, please write to

The Reprint Department
Butterworth Scientific Limited
PO Box 63 Westbury House Bury Street
Guildford Surrey GU2 5BH England

The British
Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Editorial Committee

Chairman
C W. Jamieson, *London*

Vice-Chairmen
J. L. Dawson, *London*
H. B. Devlin, *Stockton-on-Tees*

Editors
R. C. G Russell, *London*
D C. Carter, *Glasgow*

Associate Editor
A. E. Young, *London*
Statistical Consultant
G. D. Murray, *Glasgow*
Editorial Secretary
Lynne Ponjee

T. Bates, *Ashford*
K. G. Burnand, *London*
(*Surgical Research Society*)
J. D. Hardcastle, *Nottingham*
A. G. Johnson, *Sheffield*
M. R. B. Keighley, *Birmingham*
J. A. P. Marston, *London*
A. N. Nicolaides, *London*
(*Royal Colleges of Surgeons*)
I. Taylor, *Southampton*
(*Association of Surgeons*)
N. S. Williams, *London*
R. C. N. Williamson, *London*

Editorial Board

A. P. R. Aluwihare, *Sri Lanka*
E Q. Archampong, *Ghana*
J. H. Baron, *London*
J. Bergan, *USA*
K. Bielecki, *Poland*
H. Bismuth, *France*
P. C. Bornman, *South Africa*
D. Bouchier-Hayes, *Dublin*
W. H. Brummelkamp, *The Netherlands*
R. Carpenter, *Jamaica*
A Cuschieri, *Dundee*
R. Dionigi, *Italy*
B. Eklof, *Kuwait*
E. A. Elebute, *Nigeria*
J. R. Farndon, *Newcastle upon Tyne*
J. M. Fitzpatrick, *Dublin*
Sir Patrick Forrest, *Edinburgh*
W. D. George, *Glasgow*
G. R. Giles, *Leeds*
I. E. Gillespie, *Manchester*
B. C. Golematis, *Greece*
J. F. Grenier, *France*
A. Habr-Gama, *Brazil*
D. Hanania, *Jordan*
F. Harder, *Switzerland*
M. A. Hassan, *Sudan*
R. J. Heald, *Basingstoke*
G. L. Hill, *New Zealand*
T. Hirayama, *Japan*
M. Horrocks, *Bristol*
E. R. Howard, *London*
L. Hulten, *Sweden*
M. H. Irving, *Manchester*
G. G. Jamieson, *Australia*
J. Jeekel, *The Netherlands*
H.-E. Jensen, *Denmark*
Jin-Pok Kim, *Korea*
K. A. Kelly, *USA*
J. A. Mannick, *USA*
T. G. Parks, *Belfast*
A. Pausawasdi, *Thailand*
C. Pera, *Spain*
H. C. Polk, *USA*
A. T. Raftery, *Sheffield*
N. Rangabashyam, *India*
J. H. C. Ranson, *USA*
C. V. Ruckley, *Edinburgh*
S Shionoya, *Japan*
J. C. Smith, *Oxford*
K. Somasundaram, *Malaysia*
T. E. Starzl, *USA*
H. Stone, *USA*
D. E. Strandness Jr, *USA*
G. Teasdale, *Glasgow*
M. Trede, *West Germany*
D. E. F Tweedle, *Manchester*
A. Watson, *Lancaster*
R. W. Webb, *USA*
D. J. T. Webster, *Cardiff*
F. R. Wilkes, *Armed Forces*
D. Wilmore, *USA*
J. Wong, *Hong Kong*
R. F. M. Wood, *London*

The British Journal of Surgery is published monthly by Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 300966 Telegrams and Telex 859556 SCITEC G Facsimile 0483 301563 Registered office Butterworth Scientific Limited, 88 Kingsway, London WC2 6AB, UK

All queries regarding submitted papers not yet accepted for publication should be addressed to Lynne Ponjee, Editorial Secretary, Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK Telephone 0483 301439 Telegrams and Telex 859556 SCITEC G Facsimile 0483 301563

Managing Editor Sarah Graham-Campbell
Sub-Editor June Greig-Smith
Production Julia Sentance
Advertisement Sales Representative Mark Butler

UK and Overseas subscription orders should be sent to Westbury Subscription Services, PO Box 101, Sevenoaks, Kent TN15 8PL, UK Telephone 0732 885833 Telex 95678 Facsimile 0732 884079 Cable Westbury, Sevenoaks, Kent **North American orders** should be sent to Journals Fulfilment Department, Butterworths, 80 Montvale Avenue, Stoneham, MA 02180, USA Telex 880052 Telephone (617) 438 8464

The annual subscription to **The British Journal of Surgery** (12 issues) for UK readers is £65 00, single copies £6 00 and personal subscription £49 00 Overseas rates are annual subscription £78 00, single copies £8 00 and personal subscription £49 00 These prices include delivery by sea mail, air mail rates are available on request For North America rates are annual subscription £78 00, single copies £8 00, personal subscription £49 00 Copies of this journal sent to subscribers in Australasia, Bangladesh, Canada, India, Pakistan, Sri Lanka and USA are air-speeded for quicker delivery at no extra cost

Back issues prior to the current volume are available from Wm Dawson & Sons Ltd, Cannon House, Folkestone, Kent, England CT19 5EE Telephone 0303 57421

US mailing agents Mercury Airfreight International Ltd Inc Second class postage paid at Rahway, New Jersey, USA Postmaster send address corrections to *The British Journal of Surgery*, c/o Mercury Airfreight International Ltd Inc, 10B Englehard Avenue, Avenel, New Jersey 07001, USA

A microfilm version of **The British Journal of Surgery** is available Please contact University Micro Films Inc, 300 N Zeed Road, Ann Arbor, Michigan, Michigan 48106, USA

Copyright: Readers who require copies (minimum quantity 100) of papers published in this journal may either purchase reprints or obtain permission to copy from the publisher For readers in the USA, permission to copy is given on the condition that the copier pays the stated per copy fee through the Copyright Clearance Center Inc, 27 Congress Street, Salem, Massachusetts 01970, USA (617) 744 3350 for copying beyond that permitted by Sections 107 and 108 of the US Copyright Law Fees appear in the code given at the foot of the first page of each paper This journal is listed in 'Current Contents'

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the Publisher

ISSN 0007-1323

Filmset by Mid-County Press, London SW15 Printed by The Friary Press Ltd, Dorchester and London

Instructions to authors

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another Journal, has not been accepted for publication elsewhere and has not already been published. Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies (one of which must be the top copy) of original articles and other editorial matter to: *The Editor, c/o Lynne Ponjee, The Editorial Secretary, Butterworth Scientific Ltd., PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK. Telephone number: 0483 301439.*

A covering letter must be signed by all authors and must state: if an abstract of the work has been published; and whether the manuscript and/or illustrations are to be returned. Books for review should also be sent to this address.

The first named author is responsible for ensuring that any other authors have seen and approved the manuscript and are fully conversant with its contents.

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. When quoting specific materials, equipment and proprietary drugs, authors must acknowledge the manufacturer but generic names should normally be used.

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65 or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from the Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR (enclose 50p).

Typescripts

Papers should be typewritten on A4 paper (210 × 297 mm) with double spacing and 4 cm margins. Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations.

Title page

The title page should give: (1) title of the article; (2) names and initials of each author with their highest academic qualifications; (3) the department and institution to which the work should be attributed; (4) name and address of author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; (6) keywords.

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytic methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Each table with an appropriately brief title should be typed on a separate page. Illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. Three copies of all illustrations should be submitted. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full, permission having been granted by the author and by the publisher.

Text

The text should usually (but not exclusively) be organized into: introduction, patients/materials and methods, results, discussion.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text but must be clearly defined.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached.

Numbers and units

The decimal point, not a comma, is used, ie 5·7. A space and not a comma follows thousands and multiples thereof, ie, 10 000. SI units (International system of units) are to be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

Statistics

Emphasis will be placed on the correct use of statistics and the statistical methods employed should be described in the methods section of the manuscript.

References

In the text, references should be numbered consecutively by superscript: 1,2 or 1–3. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication, volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s), chapter title, edition, book title, place of publication, publisher, year of publication, page numbers, for example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In :Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag 1981: 123–63.

The British Journal of Surgery

Published by Butterworths for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Volume 75 Number 10 October 1988

LEADING ARTICLE

A time for decisions 937
D. D. Trunkey

ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND

Preduodenal mechanisms in initiating gallbladder emptying in man 940
S. Ellenbogen, S. A. Jenkins, J. S. Grime, M. Critchley, C. R. Mackie and J. N. Baxter

Surgical treatment of hepatic hydatid disease 946
J. L. Dawson, J. D. Stamatakis, M. D. Stringer and R. Williams

Cholecystokinin (CCK) provocation test: long-term follow-up after cholecystectomy 951
M. Rhodes, T. W. J. Lennard, J. R. Farndon and R. M. R. Taylor

ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis 954
J. P. Neoptolemos, D. L. Carr-Locke, N. London, I. Bailey and D. P. Fossard

A prospective comparison of the effects of placebo, ranitidine and highly selective vagotomy on 24 h ambulatory intragastric pH in patients with duodenal ulcer 961
M. J. Rogers, J. H. M. Holmfield, J. N. Primrose, the late T. Gledhill and D. Johnston

Surgical glove perforation 966
R. D. A. Dodds, P. J. Guy, A. M. Peacock, S. R. Duffy, S. G. E. Barker and M. H. Thomas

Comparison of absorbable materials for surgical haemostasis 969
S. D. Blair, C. M. Backhouse, R. Harper, J. Matthews and C. N. McCollum

Endocrine basis for the clinical presentation of hidradenitis suppurative 972
B. J. Harrison, G. F. Read and L. E. Hughes

Effects of low dose perioperative interferon on the surgically induced suppression of antitumour immune responses 976
P. C. Sedman, C. W. Ramsden, T. G. Brennan, G. R. Giles and P. J. Guillou

Cystic change and neoplasia in isolated thyroid swellings 982
E. L. Cusick, C. A. McIntosh, Z. H. Krukowski and N. A. Matheson

Renal transplantation in patients over 55 years old 984
G. Lauffer, J. A. Murie, D. Gray, A. Ting and P. J. Morris

Testicular torsion in Bristol: a 25 year review 988
J. B. Anderson and R. C. N. Williamson

Anal sensation after restorative proctocolectomy for ulcerative colitis 993
P. J. Holdsworth and D. Johnston

Physiological parameters influencing function in restorative proctocolectomy and ileo–pouch–anal anastomosis 997
M. R. B. Keighley, K. Yoshioka, W. Kmiot and F. Heyen

Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique 1003
R. Miller, G. T. Lewis, D. C. C. Bartolo, F. Cervero and N. J. McC. Mortensen

Prospective randomized trial to compare the stapled double lumen pouch and the sutured quadruple pouch for restorative proctocolectomy 1008
M. R. B. Keighley, K. Yoshioka and W. Kmiot

Abdominoperineal and anterior resection of the rectum with retrocolic omentoplasty and no drainage 1012
S. R. G. Smith, I. Swift, H. Gompertz and W. N. W. Baker

Pre-operative or postoperative colonic examination for synchronous lesions in colorectal cancer 1016
J. J. T. Tate, J. Rawlinson, G. T. Royle, F. J. Brunton and I. Taylor

Endoluminal ultrasound and computed tomography in the staging of rectal cancer **1019**
P. J. Holdsworth, D. Johnston, A. G. Chalmers, P. Chennells, M. F. Dixon, P. J. Finan, J. N. Primrose and P. Quirke

REVIEW

Preventing wound infection after appendicectomy: a review **1023**
Z. H. Krukowski, S. T. Irwin, S. Denholm and N. A. Matheson

Transverse submammary skin incision for thyroidectomy (surgical workshop) **1034**
M. A. C. Aghaji

Macro-amylasaemia as a cause of persistently raised serum amylase (case report) **1035**
P. A. Andrews and P. A. Thomas

Persisting superior mesenteric artery syndrome following ileo-anal J pouch construction (case report) **1036**
P. M. Christie, D. Schroeder and G. L. Hill

Local antiseptic treatment of infected prosthetic vascular grafts in the groin (case report) **1037**
K. T. Moran and E. R. Jewell

Rare congenital anomaly of the portal vein (case report) **1038**
A. D. Joyce and E. R. Howard

Bacteriology of mammary duct ectasia (short note) **1040**
R. J. Aitken, J. Hood, J. J. Going, R. S. Miles, A. P. M. Forrest

Recurrent laryngeal nerve palsy associated with thyroiditis (short note) **1041**
M. E. Lucarotti and R. T. J. Holl-Allen

Solitary cysts of the parotid (short note) **1043**
J. D. Maynard

CORRESPONDENCE **1044**

BOOK REVIEWS **1047**

ERRATUM **1047**

NOTICES AND ANNOUNCEMENTS **1048**

Cover picture

Lord Lister Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA)

Br. J. Surg. 1988, Vol. 75, October, 937–939

A time for decisions

The Royal College of Surgeons Commission on the Provision of Surgical Services has recently reported a retrospective examination of deaths from injury in England and Wales[1]. The four assessors concluded that the deaths of 102 patients (20 per cent) were potentially preventable. An additional 68 deaths were considered potentially preventable by three of the four assessors, which would bring the preventable death rate to 33 per cent. This figure is remarkably close to those published in the USA[2], and confirms what many leaders in British surgery had already perceived: a major deficiency exists in the care of the injured.

One obvious solution is to introduce a system of trauma care throughout the UK. A trauma system consists of four patient components (access to care, prehospital care, hospital care, and rehabilitation) and four societal components (prevention, disaster care, education, and research). Given a decision to have a trauma system, at least five of these components would involve major decisions.

Prehospital care

A major cause of preventable death within the first hour of injury relates to care provided in the prehospital setting. In the last 15 years the USA has vigorously embraced the concept of aggressive resuscitation in this early period. However, most surgeons now agree that it is impossible to stabilize the critically injured patient and that only a few techniques are truly life-saving in a prehospital setting. There is no substitute for extrication and protecting the spinal cord. Almost all agree that endotracheal intubation can be life-saving for the severely shocked patient or the unconscious patient with head injury. Application of traction splints is the only technique that can reduce 'internal' hemorrhage in the prehospital setting. All other technique that can reduce 'internal' haemorrhage in the prehospital setting. All other pneumatic antishock garment, are controversial and have yet to be proved efficacious. Many of these techniques are not universally applied to accident victims in the UK. Thus, a decision will have to be made as to the type of training offered to prehospital personnel and as to the precise nature of the life support techniques that would be of value in a country where population density is high and transport times are relatively short.

Hospital care

Once a decision has been made to establish a trauma system the more difficult decisions relate to the number of trauma centres needed, what type of surgeon should man them, and who will provide the postoperative care. In planning the number of centres, it is useful to look at rates of motor vehicle deaths and injuries. In 1983 there were 5059 such deaths in England and Wales, a rate of 10·2 per 100 000 population; this compared with a rate of 19 per 100 000 population in the USA[3]. Looked at from a different perspective, the traffic fatalities per 10^8 vehicle miles for the UK was 3·4 in 1983, whereas, in the USA it was 2·7. Nevertheless, the number of traffic fatalities in England and Wales is considerably less than in other European countries.

Since trauma centres will care for the most seriously injured, it is useful to know how many hospitalized accident victims are in a truly critical condition. Based on experience in the USA, we can predict that 10–12 per cent of such victims are critically injured and, for planning purposes, it is estimated that there are 1000 critical injuries per 10^6 population per year. Another useful calculation is that in one-half of all traffic fatalities, death is at the scene of the accident. Thus, in 1983, in approximately 2500 of the traffic fatalities death was within hospital. For every death in hospital there are at least nine critically injured patients who survive. One can predict then that approximately 25 000 people annually would be severely injured in England and Wales, a number which is consistent with the population base and the lower death rate compared with other European countries. We can further estimate that a single trauma centre should be able to care for at least 1000 critically injured patients per

0007–1323/88/100937–03$3 00

year. Thus, England and Wales should have at least 20 trauma centres. Factors such as population density, geographical considerations and regional resources would all help to determine their location.

A related issue is how to integrate the military into a civilian trauma system. Training of military surgeons must have a high priority and that training must obviously include trauma care. Thus, one could make a very strong argument that at least two or three of the twenty designated trauma centres in England and Wales should be staffed by military personnel. Another option would be to include surgical registrars from the military schools in the civilian trauma centres.

What kind of surgeon should staff the designated trauma centres? Should it be a general surgeon, an orthopaedic surgeon, or a neurosurgeon? Various countries have used different solutions. In West Germany the trauma surgeon is a combination of general surgeon and orthopaedic surgeon, but leans more heavily towards the treatment of fractures. In the USA, the trauma surgeon is more typically a general surgeon who asks specialist surgeons to see the patients when appropriate. It is my perception that the UK is unfettered by any preconceived ideas about what constitutes a 'trauma surgeon'. This might be the ideal time to plan a rational solution. Given the surfeit of registrars and paucity of consultant posts, one solution might be to give general surgeons additional training in fracture management and operative neurosurgery so as to create a bona fide trauma surgeon. Such a surgeon could care for about 80 per cent of patients with neurological injuries and the majority of those with fractures and torso trauma. Such a surgeon would be quite busy in a designated trauma centre thus solving two of the problems that vex other countries: cost efficiency and maintenance of experience. The National Health Service would have to increase the number of consultants commensurate with need in the designated trauma centres.

Perhaps the most important decision to be made regarding hospital care is who will care for the patient in the postoperative or postinjury period, and particularly in the intensive care setting. It is my perception that intensive care in the UK has been abdicated by surgeons to non-surgeons. This is both unfortunate and undesirable. It is my contention that failure to care for the surgical patient in the intensive care setting is the most powerful disincentive to know the science of surgery. Furthermore, I believe that it is imperative for optimal care that a single physician should resuscitate, operate, and look out for the patient's interest in the postoperative period. This individual can then orchestrate the various specialists involved, making sure that care is co-ordinated and properly timed, thus achieving optimal outcome. I also believe strongly that an understanding of the pathophysiology of injury leads to an understanding of immunology, physiology, wound healing, metabolism, and pharmacology. A surgical registrar who has not been exposed to the trauma patient and intensive care is incompletely trained, unqualified, and unprepared for surgical practice or specialty training. It is imperative that we do not separate critical care from general surgery.

Rehabilitation

It makes no sense to resuscitate the acutely injured patient, repair his injuries, and then not have him go back to a productive life. My perception of rehabilitation care in the UK is that it is no better than that available in the USA, which is unacceptable. Thus, another critical decision will be whether to have a regionalized rehabilitation system, possibly modelled after the one in Israel.

Education

There are at least three studies in the USA which show that many surgical residents are inadequately trained to care for the trauma patient upon completion of their training. In my multiple visits to the UK I have a similar impression of registrar training. Many are never exposed to critically injured patients and I have already commented on the inadequate experience in the intensive care setting. The Royal College of Surgeons of England has shown considerable courage in examining the trauma issue and my advice would be to continue these studies and document whether or not registrars are getting adequate exposure and experience in injury management. Similarly, the question should be asked whether or not intensive care experience is adequate.

A decision to make general surgeons the primary resource in the designated trauma centres will require some restructuring of surgical training. I am not advocating creation of a trauma subspecialty within surgery. My bias is that all general surgery registrars should gain trauma experience at some time during their training. For those general surgeons who choose trauma and critical care as a professional pathway, additional training would clearly be needed that is above and beyond current standards. I must emphasize that I am not advocating extension of registrar or senior registrar training years. A rational curriculum and programme could be designed that, within the 6–7 years training period, would equip an individual to care for the trauma patient.

Research

If we assume that a system of trauma care is adopted and 20 hospitals are designated, a minimum of three trauma centres should have basic research centres attached to them. The emphasis should still be on excellent clinical care, but research would be an integral part of the centre's activities. These research centres would require government support and funding from the Medical Research Council. The remaining 17 trauma centres would do clinical research and carry out clinical protocols. I believe that the concept of basic research is imperative if trauma education and excellence in care are to be maintained.

In conclusion, in the early 1800s Alexis de Tocqueville visited the USA and set down his classic observations on democracy in America. As an outsider he had a perspective that many insiders did not have. I am not suggesting there is an analogy to my observations on trauma care in the UK, but I would not want my observations interpreted as meddlesome. Many of these observations and solutions represent a synthesis derived from observing many trauma systems throughout the world. The surgeons of the UK have an opportunity to change a system that is currently providing suboptimal care. It is my perception that leadership within the Royal Colleges of Surgeons is optimal for bringing about positive change and making tough decisions.

D. D. Trunkey

University of Portland
3181 S.W. San Jackson Park Row
Portland
Oregon 97201
USA

1 Anderson ID, Woodford M, De Dombal FT, Irving I Retrospective study of 1000 deaths from injury in England and Wales. *Br Med J* 1988; **196**: 1305.
2. Cales RH, Trunkey DD Preventable trauma deaths: a review of trauma care systems development. *JAMA* 1985; **254**: 1059.
3. *Accident Facts 1986 Edition.* Chicago, Illinois: National Safety Council.

Association of Surgeons of Great Britain and Ireland

Br. J. Surg. 1988, Vol. 75, October, 940–945

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Harrogate on 13–15 April 1988. The President of the Association, Mr N. V. Addison, was in the chair.

The Moynihan Prize was awarded to S. Ellenbogen for the paper 'Preduodenal mechanisms in initiating gallbladder emptying in man'.

Preduodenal mechanisms in initiating gallbladder emptying in man

S. Ellenbogen,
S. A. Jenkins,
J. S. Grime*,
M. Critchley*,
C. R. Mackie and
J. N. Baxter

*Department of Surgery, University of Liverpool and * Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK*

Correspondence to:
Mr S Ellenbogen,
Department of Surgery,
Royal Liverpool Hospital,
Prescot Street,
Liverpool L7 8XP, UK

The existence of preduodenal phases of gallbladder emptying in normal volunteers was investigated by evaluating the effect of sham feeding a sandwich (chew and spit) ($n = 15$)*, the sight and smell of food followed by sham feeding a cooked meal* ($n = 15$)*, and gastric distension (intragastric balloon tube)* ($n = 9$) *on gallbladder emptying and comparing these responses with those after ingestion of a standard meal* ($n = 14$)*. A control group given no intestinal stimuli were studied to determine the frequency of spontaneous emptying during fasting* ($n = 18$)*.* $^{99\mathrm{m}}$*Tc-EHIDA (2,6 diethylphenylcarbamoylmethyliminodiacetic acid) was used as the biliary tracer. The frequency of gallbladder emptying during fasting was 0·0045/min. Thus, in any 20 min period emptying occurred spontaneously in only about 1 in 11 volunteers. Significant emptying* (>5 *per cent over 20 min) occurred in 8 out of 15 volunteers after sham feeding a sandwich* ($P < 0{\cdot}001$ versus *control), in 8 out of 15 volunteers after sham feeding a cooked meal* ($P = 1{\cdot}0$ versus *sandwich sham feed, n.s.), in 6 out of 9 volunteers after gastric distension* ($P < 0{\cdot}001$ versus *control) and in 14 out of 14 volunteers after meal ingestion. The rate of emptying was significantly greater in the gastric distension and meal ingestion groups compared with other groups* ($P < 0{\cdot}05$)*. However, the emptying rate after sham feeding was not significantly different from spontaneous gallbladder emptying* ($P > 0{\cdot}05$*, n.s.). There was no significant difference in time to onset of emptying between the four stimulus groups* ($P > 0{\cdot}05$*, n.s.). These results suggest that pre-duodenal stimuli can evoke gallbladder emptying in man, although the precise physiological significance of this phenomenon remains to be established.*

Keywords: Gallbladder emptying, preduodenal mechanisms, cholescintigraphy

It is generally accepted that the principal function of the gallbladder is to store and concentrate bile during the interdigestive state in preparation for the arrival of nutrients to the duodenum. Gallbladder contraction is thought to be initiated by cholecystokinin released from small bowel enterocytes and results in the delivery of concentrated bile to the duodenum to facilitate emulsification and subsequent absorption of fat. This traditional hypothesis is simplistic and does not explain the physiological role of gallbladder emptying in the interdigestive period and in the period before nutrients enter the small bowel. Thus, there is now convincing evidence in man[1–4] and in experimental animals[5–9] to suggest that emptying occurs during the interdigestive state. Furthermore, in the digestive state there is some evidence to suggest that preduodenal mechanisms initiate emptying in the dog[10–12] and in man[3,13,14] before food enters the small bowel. Possibly, perturbation of preduodenal gallbladder emptying may explain some of the undesirable effects of gastric surgery such as the increased risk of gallstones[15], bile vomiting and malabsorption[16–18]. Therefore, the purpose of this study was to evaluate the effect of cephalic, oral and gastric stimuli on gallbladder emptying in normal healthy volunteers and to compare these responses with those after

0007–1323/88/100940–06$3 00

Table 1 *Study protocol and details of volunteers studied*

	Control	Sandwich sham feed	Gastric distension	Cooked meal sham feed	Meal ingestion
n	18	15	9	15	14
Mean age (years)	29	26	24	27	21
Age range (years)	19–49	20–39	20–40	19–62	18–24
Male:female	15 M:3 F	8 M:7 F	6 M:3 F	10 M:5 F	8 M:6 F
Experimental time sequence					
−7 h	Fast	Fast	Fast	Fast	Fast
−2 h	Nasogastric tube	Nasogastric tube	Nasogastric tube	No nasogastric tube	No nasogastric tube
0	^{99m}Tc-EHIDA, IV	^{99m}Tc-EHIDA, IV	^{99m}Tc-EHIDA, IV	^{99m}Tc-EHIDA, IV	^{99m}Tc-EHIDA, IV
Intestinal stimulus	(No intestinal stimulation)	Sham fed a sandwich with a choice of filling (10 min)	Gastric distension by inflation of an intragastric balloon (20 min)	Sight and smell of food in preparation (7 min, range = 4–12 min) followed by sham feeding a cooked meal of choice (10 min)	Sight and smell of food in preparation (9 min, range = 7–10 min) followed by ingestion of a standard meal (10 min)

IV, intravenous

ingestion of a standard meal. A group of normal volunteers studied without intestinal stimulation were used to calculate the frequency of spontaneous emptying during the interdigestive period.

Patients and methods

This study was approved by the Royal Liverpool Hospital Ethical Committee (April 1984). Permission to use radiopharmaceuticals was given by the Administration of Radioactive Substances Advisory Committee (1984) Informed consent was obtained from all volunteers before participating in the study. Studies were performed on normal healthy volunteers who had no history of gastrointestinal symptoms and were not receiving any form of medication at the time of study.

Measurement and validation of gallbladder emptying

Gallbladder emptying was measured quantitatively by ^{99m}Tc-EHIDA (2,6 diethylphenylcarbamoylmethyliminodiacetic acid) cholescintigraphy as described by Baxter *et al.*[3] using a Searle Large Field of View gamma camera (G. D. Searle, Unithoorne, The Netherlands) fitted with a low energy all purpose collimator and linked to a computer system (Digital PDP 11/34, Maynard, Massachusetts, USA). Data were continuously acquired at the rate of 1 frame/min and stored on hard magnetic discs for subsequent analysis.

To analyse a study, regions of interest were drawn around the gallbladder, stomach and a representative portion of liver for liver overlap and background subtraction. Using a novel software program, the gallbladder was aligned in all frames to avoid inaccuracies due to movement of the organ in a horizontal or vertical plane out of the region of interest Time–activity curves were generated and corrected for isotope decay. The error due to movement of the gallbladder in an anterior–posterior direction was assessed in five normal volunteers (mean age, 28 years (range 19–34), 3 men.2 women) using a laterally placed gamma camera to measure movement of the gallbladder relative to an anterior surface marker. The maximal cell count within the gallbladder and surface marker were considered to be the centres of activity and relative movement between the two were measured in a 10 min period before and for 20 min after ingestion of a fatty meal. The change in sensitivity of the system was assessed by suspending a small gallbladder phantom filled with ^{99m}Tc in a water bath at various depths, and measuring the counts emitted from the phantom ($n = 6$). From this experiment the equivalent change in sensitivity due to movement of the gallbladder relative to the surface marker was calculated. This change in sensitivity due to gallbladder movement in an anterior–posterior plane was used to define significant emptying.

Cumulative emptying over a specific time period (gallbladder ejection fraction) was calculated as the decrease in activity over the gallbladder region of interest divided by the initial maximum activity and multiplied by 100 in order to express gallbladder emptying as a percentage[3]

Study protocol (Table 1)

Each study was preceded by a 7 h fast. In the majority of volunteers, except those indicated below, a FG8 nasogastric tube was inserted 2 h before scintigraphic imaging of the gallbladder. The volunteer then lay semi-recumbent under the gamma camera and was given 40 MBq of ^{99m}Tc-EHIDA intravenously. By observing the accumulation of radioactivity in the gallbladder on a colour monitor the appropriate stimulus could be given when counts within the organ were relatively constant, usually about 50 min after the administration of the isotope.

A control group and four stimulus groups of volunteers were studied. The control group ($n = 18$; mean age, 29 years (range, 19–49); 15 men.3 women) were observed without gastrointestinal stimulation for a variable time period, 2–5 h, dependent on the tolerance of the volunteer. The average time for visualization of the gallbladder was 20 min after intravenous injection of ^{99m}Tc-EHIDA, maximum counts occurring approximately 30 min later. From these data, the frequency of spontaneous emptying during the interdigestive state for each volunteer was calculated as follows

$$\frac{\text{Number of gallbladder emptying episodes}}{\text{Length of study} - 20\ \text{min}}$$

The mean frequency of emptying from this control group (gallbladder emptying episodes/min) was used to calculate the number of volunteers who would be expected to empty their gallbladder spontaneously in each stimulus group during the stimulus period. Statistical comparison was made between the number of volunteers expected to empty their gallbladder and the actual number of volunteers emptying their gallbladder in each stimulus group during the stimulus period.

Cephalic and oral phases of emptying were investigated in 2 groups of 15 volunteers each. The first group of volunteers (mean age, 26 years (range, 20–39); 8 men:7 women) were sham fed (chew and spit technique) a sandwich with a choice of filling for a 10 min period Sandwiches were prepared in a separate area so that volunteers could neither see nor smell the food until it was presented to them. The second group of 15 volunteers (mean age, 27 years (range, 19–62), 10 men 5 women), including 6 volunteers from the first stimulus group, were studied without a nasogastric tube and sham fed an appetising meal of choice, e.g. steak, mushroom and onions which was cooked in front of them for 4–12 min before sham feeding in the form of a sandwich for 10 min. In all sham-feed studies the food was coated with 5 MBq of ^{99m}Tc-Bran (prepared as described by Sagar *et al.*[19]) to detect accidentally swallowed food

The gastric phase was investigated in nine volunteers (mean age, 24 years (range, 20–40), 6 men 3 women). In these volunteers the nasogastric tube had a condom tied around the distal orifice. Gastric distension was performed by inflating the condom with 500 ml of tap water at 37°C over 10 min After a further 10 min period of distension the balloon was rapidly deflated.

A fourth stimulus group of volunteers ($n = 14$; mean age, 21 years (range, 18–24), 8 men:6 women) were unencumbered with a nasogastric tube and were given a standard solid meal of steak (8 oz), mushroom (2 oz), onion (4 oz), 1 slice of bread and butter (1 oz), cooked in front of the volunteer for 7–10 min before ingestion over a 10 min period.

Table 2 *Movement of the gallbladder in an anterior–posterior direction relative to a surface marker measured over a 10 min period before and 20 min after ingestion of a fatty meal* (n = 5)

Volunteers	Mean pixel movement 10 min before fatty meal	Mean pixel movement 20 min after fatty meal	Equivalent change in sensitivity from phantom experiment (%) 10 min before fatty meal	Equivalent change in sensitivity from phantom experiment (%) 20 min after fatty meal	Actual change in gallbladder counts relative to peak counts (%) 10 min before fatty meal	Actual change in gallbladder counts relative to peak counts (%) 20 min after fatty meal
1	0·2	0·6	1·5	4·6	8·4	43·5
2	0·3	0	2·56	0	2·2	0
3	1·1	0·75	8·3	5·7	15·0	62·0
4	0·2	0·2	1·5	1·5	20·0	32·0
5	0·5	0·5	3·9	3·9	2·1	14·0
Mean ± s.e.m.	0·46 ± 0·17 (0·29 ± 0·13 cm)	0·41 ± 0·14 (0·26 ± 0·12 cm)	3·6 ± 1·3	3·14 ± 1·4	9·5 ± 3·5	30·3 ± 10·9

For comparison, the actual change in gallbladder counts relative to peak counts following the fatty meal is shown

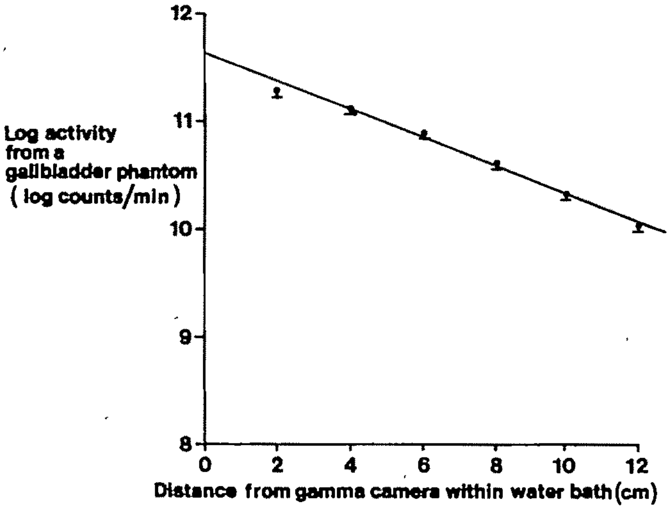


Figure 1 *Change in activity from a gallbladder phantom at various depths within a water bath* (n = 6). *By log transformation and least square analysis, the linear attenuation coefficient* (μ) *was derived, 0·12/cm. From the equation* $C_x = C_0 e^{-\mu x}$ *where* C_x *= counts at depth x and* C_0 *= counts at a reference depth, the equivalent change in sensitivity (per cent) owing to movement of the gallbladder relative to a surface marker was calculated*

Table 3 *Fasting gallbladder emptying, number of episodes and calculated gallbladder emptying rate*

Subject	Number of GBE episodes	Length of study (min)	GBE rate (per min)
1	0	182	0
2	2	130	0·018
3	1	230	0·0048
4	3	278	0·012
5	0	240	0
6	1	202	0·0055
7	1	168	0·0068
8	0	235	0
9	0	258	0
10	2	298	0·0072
11	1	266	0·0041
12	0	142	0
13	0	238	0
14	0	138	0
15	0	154	0
16	1	210	0·0053
17	1	140	0·0083
18	2	238	0·0092
Mean ± s.e.m.			0·0045 ± 0·0012

GBE, gallbladder emptying

Statistical analysis

Statistical differences between the stimulus groups and the control group were calculated using the Poisson test, and between the stimulus groups by Fisher's exact test. Comparison between emptying curves was performed with Tukey's 'Wholly Significant Difference' test and time to onset of emptying between stimulus groups by analysis of variance. Results are expressed as mean ± s.e.m.

Dosimetry

Dosimetry calculations using Medical Internal Radiation Dose Committee tables resulted in the following doses of radiation, 0·5 mGy to the whole body and 4 mGy to the target organ.

Results

Definition of significant gallbladder emptying

Movement of the gallbladder in an anterior–posterior plane ($n = 5$) was 0·46 ± 0·17 pixels (0·29 ± 0·13 cm) over a 10 min period before ingestion of a fatty meal, and 0·41 ± 0·14 pixels (0·26 ± 0·12 cm) over a 20 min period after ingestion of the fatty meal (*Table 2*). From the phantom study, the linear attenuation coefficient (μ) was 0·12/cm (*Figure 1*). The equivalent change in sensitivity due to movement of the gallbladder relative to the surface marker was 3·6 ± 1·3 and 3·14 ± 1·4 per cent respectively. Therefore, to minimize this potential error, significant emptying was defined as a gallbladder ejection fraction of >5 per cent over 20 min commencing during the stimulus period.

Control group studies (interdigestive phase) (Table 3)

Only 10 out of 18 volunteers in the control group significantly emptied their gallbladder. Fifteen emptying episodes were observed in these ten volunteers. The frequency of emptying during the fasting state was calculated as 0·0045 ± 0·0012/min.

Sham-feed studies (cephalic and oral phases) (Figure 2)

Eight out of fifteen volunteers who were sham fed a sandwich for 10 min emptied their gallbladder. When compared with the control group result (0·7 out of 15 volunteers), this result was statistically significant ($P < 0·001$ Poisson test). Of the 15 volunteers who were sham fed a meal cooked in front of them, only 8 started to empty their gallbladder during the stimulus period. This result was not significantly different from the sandwich sham-feed group result ($P = 1·0$ Fisher's exact test, n.s.). Furthermore, emptying commenced in six out of these eight volunteers during the period of food preparation before sham feeding. Of the six volunteers sham fed both a sandwich and a cooked meal, one out of six emptied their gallbladder in response to a sandwich sham feed whereas three emptied their gallbladder in response to the cooked meal sham

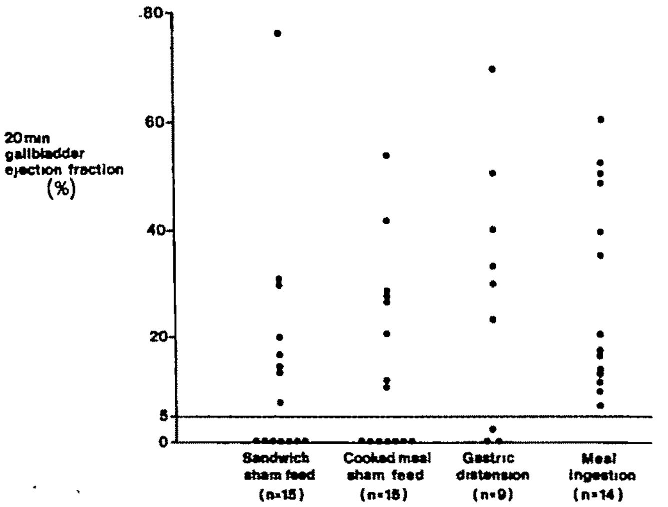


Figure 2 *Twenty minute gallbladder ejection fraction measured in the four stimulus groups of volunteers. Eight out of fifteen volunteers sham fed a sandwich and six out of nine volunteers following gastric distension significantly emptied their gallbladder (>5 per cent over 20 min). These results were significantly different from the control group result ($P<0·001$, Poisson test). Enhancement of the cephalic stimulus with the cooked meal sham fed did not increase the gallbladder emptying response ($P>0·5$, Fisher's exact test, n.s.). All volunteers allowed to ingest a standard meal emptied their gallbladder*

feed ($P=0·55$ Fisher's exact test, n.s.). A significant increase in activity in a gastric region of interest, which may have signified that some of the sham fed food was swallowed, was observed in only 5 out of 30 sham-feed studies. In two of these studies emptying did not occur, whilst in the remaining three studies emptying commenced during food preparation alone and before sham feeding commenced. Thus, the increased activity measured in the gastric region of interest was probably due to reflux of radioactive bile from the duodenum into the stomach.

Gastric distension studies (gastric phase) (Figure 2)

During the 20 min period of gastric distension six out of the nine volunteers emptied their gallbladder. When compared with the control group (0·8 out of 9 volunteers) this result was statistically significant ($P<0·001$ Poisson test) and could not have resulted from spontaneous emptying.

Meal ingestion studies (digestive phase) (Figure 2)

Following meal ingestion, all 14 volunteers eventually emptied their gallbladder, 10 volunteers during the first 20 min of meal ingestion (4 during meal preparation alone). Compared with the results from the control group (1·3 out of 14 volunteers) this result was statistically significant ($P<0·001$ Poisson test).

Gallbladder emptying curves (Figure 3)

In all five groups of volunteers, emptying closely resembled a single exponential function. Comparing the gradients of the emptying curves (log gallbladder ejection fraction *versus* time) within each group emptying rate was individual ($P<0·05$ Tukey's 'Wholly Significant Difference' test). However, comparison of the gradients of the mean emptying curves (log gallbladder ejection fraction *versus* time) for the five groups studied indicated that the rate was significantly greater following gastric distension (−0·00706) and meal ingestion (−0·00674) compared with the other groups ($P<0·05$ Tukey's 'Wholly Significant Difference' test). The rates following sham feeding a cooked meal (−0·00295) and following sham feeding a sandwich (−0·00276) were not significantly greater than that for spontaneous emptying (−0·00272) ($P>0·05$ Tukey's 'Wholly Significant Difference' test, n.s.).

Time to onset of gallbladder emptying

There were no statistical differences between the times to onset of gallbladder emptying following any of the stimuli: 2·4 ± 0·9 min (sandwich sham fed), 4·5 ± 1·6 min (cooked meal sham fed), 9·8 ± 1·8 min (gastric distension), 14·6 ± 3·4 min (meal ingestion) ($P>0·05$, analysis of variance, n.s.).

Discussion

Of the two non-invasive methods for measuring gallbladder emptying, scintigraphy and ultrasound, scintigraphy is the more

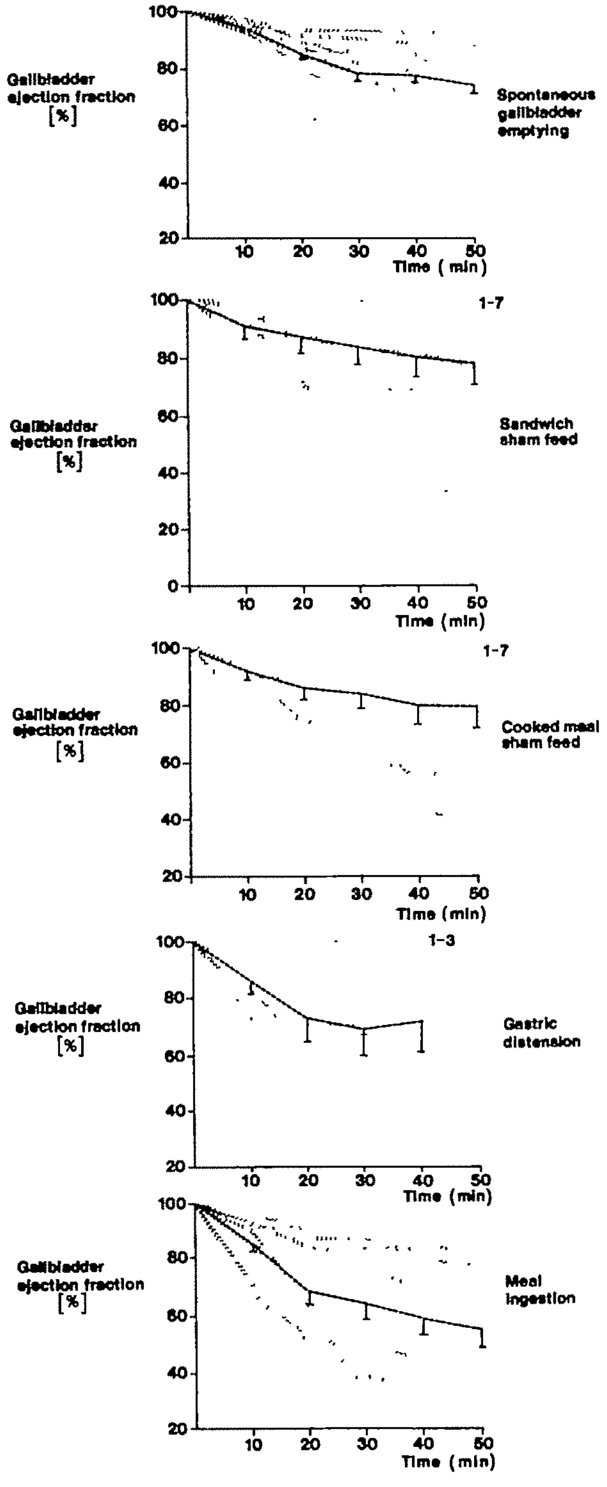


Figure 3 *Individual gallbladder emptying curves* (·····) *in the control and four stimulus groups of volunteers studied. The mean gallbladder emptying curves* (——) *for each group is also shown Vertical bars represent the s.e.m*

accurate and reproducible[3,20,21]. Therefore, in this study planar cholescintigraphy was used to measure emptying. Furthermore, in this study onset of significant emptying was closely defined since movement of the gallbladder towards and away from the gamma camera could have been interpreted as gallbladder emptying. Recent studies using a dual headed gamma camera indicated that this error was potentially large[22]. However, our studies in five normal volunteers using a laterally positioned gamma camera and a surface marker indicated that this potential error was small, 3·14 ± 1·4 per cent over 20 min, and these observations formed the basis of our definition of significant emptying, i.e. >5 per cent over 20 min.

To evaluate the significance of the emptying response to various stimuli, the frequency of spontaneous gallbladder emptying in the interdigestive state must be taken into account. Numerous studies have shown that emptying does occur in the interdigestive state[1–9] and may be a component of the secretory phase of the interdigestive migrating motor complex. In the present study a control group of volunteers was studied under similar conditions to the sandwich sham-feed and gastric distension stimulus groups to calculate the frequency of interdigestive emptying under these conditions and to allow a statistical comparison to be made. Interdigestive gallbladder emptying was infrequent and, despite prolonged periods of observation, was not present in many normal volunteers. The frequency was 0·0045/min, i.e. in any 20 min period interdigestive emptying will occur in about 1 out of 11 volunteers studied.

In man there have been several reports of an oral phase of gallbladder emptying. Fisher *et al.* using a cholescintigraphic technique similar to that used in the present study demonstrated that sham feeding caused gallbladder emptying in 10 volunteers, the rate of emptying being similar in the first hour to that after meal ingestion[13]. Using real time ultrasound, Hansen and his colleagues demonstrated a small consistent reduction in gallbladder volume following sham feeding which approximated to about one-third of the gallbladder volume reduction observed after ingestion of a liquid meal[14]. The results of the present study confirm these previous observations in man that sham feeding a sandwich or a cooked meal initiates emptying; the rate following sham feeding was about 50 per cent of that following ingestion of a solid meal and was similar to the rate during the interdigestive state.

Although cephalic phases of gastric[23,24] and pancreatic secretion[23,25,26] are well described in man, those of gallbladder emptying are less well documented. Puestow measured bile entry into the duodenum in the dog before and after cholecystectomy and showed that the sight and smell of food was sufficient to initiate emptying[11] In the present study the majority of volunteers who emptied their gallbladder in response to cooking followed by sham feeding a meal did so during the cooking of the meal, indicating that the sight and smell of food alone was sufficient to initiate emptying. Therefore, the results of the present study strongly suggest that gallbladder emptying can be initiated by cephalic stimuli.

A gastric phase has been demonstrated in the dog but not in man. Debas and Yamagishi demonstrated that distension of an antral pouch in the dog resulted in gallbladder emptying[12]. Using a gastric distension stimulus in man we have also demonstrated emptying which, over 40 min, is similar in magnitude to the response to ingestion of a solid meal.

In the control and stimulus groups some volunteers did not empty their gallbladder. In the control group regular emptying and subsequent refilling of the gallbladder during the interdigestive state may be important in digesting residual small bowel contents, in regulating small bowel motility, and perhaps most importantly in preventing the supersaturation of gallbladder bile and gallstone formation. It is possible that those volunteers who do not regularly contract their gallbladders during fasting may be more prone to gallstone formation. The reason why gallbladder emptying did not occur in some volunteers in response to preduodenal stimuli is not known. Failure to reach a threshold stimulus was probably not the reason for the lack of response since gallbladder emptying did not occur when oral stimulation was increased by enhancing the stimulus, i.e. sight and smell of food in preparation. Furthermore, the presence of a nasogastric tube did not significantly reduce the emptying response to oral stimulation. Inhibitory influences on gallbladder contraction such as nutrients in the colon[27] or bile instilled into the small bowel[28,29] have been demonstrated, and may have prevented gallbladder emptying in those volunteers who did not respond to preduodenal stimuli. However, it was not possible in this study to evaluate the extent of these potentially inhibitory stimuli. Although all volunteers studied were normal a further possibility for the absence of gallbladder emptying response to preduodenal stimuli could have been a pathological absence of the enterocholecystic pathway. However, this seems unlikely since gallbladder emptying occurred in one out of six volunteers sham fed a sandwich, whereas preparation of a cooked meal before sham feeding evoked a response in 3 out of the same 6 volunteers.

The early delivery of concentrated bile to the duodenum following ingestion of a meal may be important for priming the enterohepatic circulation and altering small bowel motility[30,31] both of which may be important in optimizing digestion and absorption of nutrients. It is possible that the pathological absence of preduodenal mechanisms of gallbladder emptying may occur following gastric surgery and may contribute to some of the side-effects such as bile vomiting and malabsorption.

Gallbladder contractions are influenced both by hormones, especially cholecystokinin, and by autonomic nerves, in particular the cholinergic fibres. Fisher *et al.* demonstrated that the oral phase of gallbladder emptying was inhibited by atropine and vagotomy and concluded that the mechanism responsible for this phase was a vagal cholinergic reflex[13]. Debas and Yamagishi denervated the antral pouch in their dog model and demonstrated that the response to antral distension was abolished indicating that the gastric phase in the dog was cholinergically mediated[12]. However, neither group measured cholecystokinin levels. Anagnostides *et al.* investigating an oral phase of pancreatic secretion showed that there was no significant rise in the circulating levels of cholecystokinin or gastrin in response to sham feeding a ham sandwich[32]. Preduodenal phases of gallbladder emptying could be evoked directly via local receptors to nutrient stimulation. Alternatively, it is possible that gastric secretions produced by cephalic, oral and gastric stimuli may enter the duodenum and initiate gallbladder emptying via cholecystokinin released from small bowel enterocytes or via an enterocholecystic nervous reflex. However, this explanation seems unlikely since neither oral stimuli[32] nor gastric distension[33] in man cause a significant rise in circulating gastrin levels. Furthermore, Fisher *et al.* observed that sham feeding stimulated gallbladder emptying even when gastric secretions were aspirated[13] although it is conceivable that small amounts of acid may have entered the duodenum. Anagnostides *et al.* circumvented this problem in their investigation of a cephalic phase of pancreatic secretion by inhibiting acid secretion with cimetidine[32]. Pancreatic enzyme response to sham feeding was reduced by cimetidine indicating that duodenal acidification was contributing to the pancreatic enzyme response to oral stimuli. In the present studies, swallowed food may have contributed to the observed gallbladder emptying response. However, in none of those volunteers in which emptying occurred after sham feeding did swallowed food appear to contribute to the initiation of gallbladder emptying.

Clearly preduodenal mechanisms of gallbladder emptying do play a significant part in the response to meal ingestion. Further studies are required to elucidate the mechanisms of these preduodenal phases, to investigate the inhibitory influences on the gallbladder and to evaluate the changes following gastric surgery.

Acknowledgements

This investigation was supported by a Medical Research Council Grant (No. G84160355B)

References

1. Svenberg T, Christofides ND, Fitzpatrick ML, Areola-Ortiz F, Bloom SR, Welbourne RB. Interdigestive biliary output in man: relationship to fluctuations in plasma motilin and effect of atropine. *Gut* 1982; **23**: 1024–8.
2. Kraglund K, Hjermind J, Jensen FT *et al.* Gallbladder emptying and gastrointestinal cyclic motor activity in humans. *Scand J Gastroenterol* 1984; **19** 990–4.
3. Baxter JN, Grime JS, Critchley M, Shields R Relationships between gastric emptying of solids and gallbladder emptying in normal volunteers *Gut* 1985, **26**: 342–51.
4. Toouli M, Bushell G, Stevenson J *et al.* Gallbladder emptying in man related to fasting duodenal migrating motor contractions. *Aust NZ J Surg* 1986; **56** 147–53.
5. DiMagno EP, Hendricks JC, Go VLW, Dozois RR Relationships among canine fasting pancreatic and biliary secretions, pancreatic duct pressure and duodenal type III motor activity—Boldyreff revisited. *Dig Dis Sci* 1977; **24**: 684–93.
6 Traynor OJ, Dozois RR, DiMagno EP. Canine interdigestive and postprandial gallbladder motility and emptying. *Am J Physiol* 1984; **246**· G426–32.
7 Itoh Z, Takahashi I. Periodic contractions of the canine gallbladder during the interdigestive state. *Am J Physiol* 1981, **3**. G183–9.
8 Takahashi I, Dodds WJ, Hogan WJ *et al* Variations in gallbladder volume and pressure during fasting and after feeding in the conscious opossum. *Gastroenterology* 1983; **84**: 1329 (abstract).
9. Nally CV, McMullin LJ, Clanachan AS, Scott GW Periodic gallbladder contraction maintains bile acid circulation during the fasting period; a canine study. *Br J Surg* 1987; **74**: 1134–9.
10. McMaster PD, Elman R. On the expulsion of bile by the gallbladder, and a reciprocal relationship with sphincter activity. *J Exp Med* 1926; **44**: 173–98.
11 Puestow CB The discharge of bile into the duodenum *Arch Surg* 1931, **23**. 1013–29.
12 Debas HT, Yamagishi T. Evidence for a pyloro-cholecystic reflex for gallbladder contraction. *Ann Surg* 1979; **190**. 170–5.
13 Fisher RS, Rock E, Malmud LS Gallbladder emptying response to sham feeding in humans *Gastroenterology* 1986, **90**: 1854–7
14. Hansen WE, Maurer H, Haberland H. The effect of sham-feeding on gallbladder volume and circulation of bile acids. *Hepatogastroenterology* 1982; **29**· 108–10.
15. Tomkins RA, Kraft AR, Zimmerman E, Lichtenstein JE, Zollinger RM Clinical and biochemical evidence of increased gallstone formation after complete vagotomy. *Surgery* 1972, **71**· 196–200.
16. Wastell C, Ellis H. Faecal fat excretion and stool colour after vagotomy and pyloroplasty. *Br Med J* 1966; **i**: 1194–7.
17. Cox AG. The outcome of truncal vagotomy and a drainage procedure. In: Cox AG, Williams JA, eds. *Vagotomy in Trial.* London: Heinemann Medical Books, 1973: 67–83.
18. Edwards JP, Lyndon PJ, Smith RB *et al* Faecal fat excretion after truncal, selective and highly selective vagotomy for duodenal ulcer. *Gut* 1974, **15**· 521–5
19 Sagar S, Grime JS, Little W *et al.* ^{99}Tc^{m} labelled bran—a new agent for measuring gastric emptying. *Clin Radiol* 1983; **34** 275–8
20. Everson GT, Braverman DZ, Johnson ML, Kern F. A critical evaluation of real time ultrasonography for the study of gallbladder volume and contraction. *Gastroenterology* 1980, **79**. 40–6.
21. Krishnamurthy GT, Bobba VR, Kingston E. Radionuclide ejection fraction a technique for quantitative analysis of motor function of the human gallbladder. *Gastroenterology* 1981; **80**. 482–90.
22. Jazrawi RP, Kupfer RM, Bridges C, Joseph A, Northfield TC Assessment of gallbladder storage function in man. *Clin Sci* 1983, **65**: 185–91.
23. Pavlov IP. The centrifugal (efferent) nerves to the gastric glands and the pancreas. In: *The Work of the Digestive Glands.* Translated by Thompson WH. Philadelphia: Charles Griffin and Company Ltd, 1910: 48–59.
24. Feldman M, Richardson CT. Role of thought, sight, smell and taste of food in the cephalic phase of gastric acid secretion in humans *Gastroenterology* 1986; **90**: 428–33.
25 Sarles H, Dani G, Prezelin G, Souville C, Figarella C. Cephalic phase of pancreatic secretion in man. *Gut* 1968, **9** 214–21
26. Novis BH, Bank S, Marks IN. The cephalic phase of pancreatic secretion in man. *Scand J Gastroenterol* 1971; **6** 417–22
27 Owyang C, Green L, Radar R Colonic inhibition of pancreatic and biliary secretion *Gastroenterology* 1983; **84**· 470–5.
28. Malagelada J, DiMagno EP, Summerskill WHJ. Regulation of pancreatic and gallbladder function by intraluminal fatty acids in man. *J Clin Invest* 1976; **58**: 493–9.
29. Bjornsson DG, Maton PN, Fletcher DR, Chadwich VS. Effects of duodenal perfusion with sodium taurocholate on biliary and pancreatic secretion in man. *Eur J Clin Invest* 1982; **12**: 97–105.
30. Penagini R, Misiewicz JJ, Frost G. Glycochenodeoxycholic (GCDC) and glycocholic (GC) acids infused in the human jejunum inhibit small bowel motility and transit. *Gut* 1987; **28** A1399–40 (abstract)
31. Penagini R, Spiller RC, Misiewicz JJ, Frost PG Feedback regulation of transit and motility in the human jejunum and ileum by ileal infusion of glycochenodeoxycholic acid (GCDC) *Gut* 1987; **28** A1398 (abstract)
32. Anagnostides A, Chadwick VS, Selden AC, Maton PN. Sham feeding and pancreatic secretion. Evidence for direct vagal stimulation of enzyme output. *Gastroenterology* 1984, **87**. 109–14
33. Soares EC, Zaterka S, Walsh J. Acid secretion and serum gastrin at graded intragastric pressures in man. *Gastroenterology* 1977; **72**. 676–9.

Br. J. Surg. 1988, Vol. 75, October,
946–950

Surgical treatment of hepatic hydatid disease

J. L. Dawson,
J. D. Stamatakis*,
M. D. Stringer and
R. Williams†

*Department of Surgery and †Liver Unit, King's College Hospital, Denmark Hill, London SE5 9RS, and *Princess of Wales Hospital, Bridgend, Wales CF31 1RQ, UK*

Correspondence to:
Mr J. L. Dawson

The results of surgery in 48 patients with hepatic hydatid disease are described. In 26 out of 32 patients with uncomplicated cysts, conservative surgery with obliteration of the cyst cavity by omentoplasty gave satisfactory results. In contrast, 16 patients with cysts complicated by pyogenic infection or cholangitis required a variety of surgical procedures, including prolonged tube drainage, exploration of the common bile duct, sphincterotomy/plasty and hepatojejunostomy to achieve a satisfactory outcome. The group with complicated cysts also had a much longer postoperative stay (median 30 days) than those with uncomplicated cysts (median 14 days). Two patients died: in one, post-mortem examination revealed carcinoma in the wall of the cyst.

Keywords: Echinococcosis, hepatic, omentum, surgery

Hydatid disease is a major world health problem. The disease is endemic in areas where close and continuous contact exists between domesticated dogs, the principal definitive hosts, and sheep, which are the commonest intermediate hosts of the dog tapeworm, *Taenia echinococcus granulosus*. Incidental human infestation commonly leads to cyst formation in the liver. Symptoms arise from local pressure, leakage, infection or rupture into the biliary tree. Surgical management of hepatic hydatid cysts ranges from formal hepatic resection to partial cystectomy with omentoplasty. We report an 18-year experience employing a conservative surgical approach to these patients.

Patients and methods

During the years 1970–1988, 48 patients with hepatic hydatid disease underwent surgical treatment at King's College Hospital, London (J.L.D.), and Princess of Wales Hospital, Bridgend (J.D.S.): 26 were referred from endemic areas overseas, 13 were from South Wales and 7 of the remaining 9 had travelled through areas where the disease is prevalent (*Figure 1*). Patients' ages ranged from 6 to 78 (median 49) years and sex distribution was equal (25 male and 23 female). Of the 48 patients, 13 had undergone previous hepatobiliary surgery before referral. In addition, two patients had undergone percutaneous procedures with disastrous results (one biliary peritonitis and one anaphylaxis).

Clinical features

Infection causing jaundice, abdominal pain and fever was the presenting feature in 16 patients: 4 had pyogenic infection of the cyst (only 1 had previous surgery) and 12 had cholangitis. Twenty-two patients presented with abdominal discomfort, usually in the right hypochondrium, and an asymptomatic abdominal mass was discovered by chance in eight others. Urticaria and anaphylaxis led to the diagnosis in two patients. In one of these, symptoms followed percutaneous aspiration of an hepatic cyst diagnosed by ultrasound scan. In the second case the patient herself recognized urticaria similar to that which she had experienced before previous surgery for pulmonary hydatid disease.

Diagnosis

Pre-operative diagnosis of an hydatid cyst was made from the clinical features, together with various combinations of investigations including plain radiography (demonstrating cyst calcification in 12 patients), ultrasound and computerized tomographic (CT) scanning, angiography and serology. Ultrasound and CT scanning were accurate in locating the site, size and number of intrahepatic cysts, together with contained daughter cysts (*Figure 2*). However, one case diagnosed as an hepatic hydatid cyst eventually proved to be a suprarenal hydatid cyst buried within the right lobe of the liver (*Figure 3*), a potential source of confusion that we have also observed with suprarenal tumours.

In 32 patients (70 per cent) cysts were located in the right lobe of the liver, 6 were in the left lobe and 8 patients had multiple cysts. One patient had daughter cysts in the common bile duct with no identifiable intrahepatic cyst and one had a suprarenal hydatid cyst.

In patients with a history of jaundice, endoscopic retrograde cholangiopancreatography (ERCP) and/or operative cholangiography were also performed. ERCP demonstrated daughter cysts in the common bile duct in three cases and a communication between the cyst and the biliary tree in a further three (*Figures 4* and *5*). Despite antibiotic prophylaxis, one patient developed bacterial cholangitis following this procedure which probably contributed to his troublesome postoperative course (see below).

Serology was not always helpful, the Casoni test being positive in 7 out of 8 patients tested (now no longer used), the complement fixation test (CFT) positive in 24 out of 30 and the enzyme-linked immunosorbent assay (ELISA) positive in 9 out of 11 cases.

Surgical treatment

The operative management in this series was conservative. Exposure of the liver was obtained through a right subcostal incision extending to the left when required. A posterior approach with rib resection was used on three occasions, once for the primary operation and twice for revision procedures to drain pus. After exploration of the abdomen, the liver was mobilized and adhesions to the cyst divided. When firmly adherent to the diaphragm, particular care was required during the dissection to avoid entering the pleural cavity. The area around the cyst was then carefully isolated by gauze packs soaked in a scolicidal agent. Whenever possible, initial cyst aspiration and replacement with scolicide was performed but this proved impossible with large cavities filled with daughter cysts. A Mayo Oschner trocar was used for evacuation, after which the edge of the collapsing cyst was grasped with tissue forceps and the sucker tubing itself inserted into the cavity to remove the numerous daughter cysts, the largest requiring removal by sponge-holding forceps. All laminated membrane was removed and the cavity carefully wiped with scolicide-soaked swabs. No attempt was made to remove the pericyst except from the surface of the liver in order to allow a generous aperture for entry of the omental graft. Sites of biliary leakage in the cyst wall were not sutured as early experience showed that this was almost impossible to do with accuracy. Whenever possible, a pedicled omental graft was fashioned and drawn up into the cavity to fill it loosely, the graft being held in position by catgut sutures. A drainage tube was laid alongside to provide egress for any biliary leakage.

Following the introduction of mebendazole, patients were given this drug pre-operatively and for 3 weeks postoperatively. More recently, we have used albendazole.

Results

The patients are best analysed in three groups: (1) uncomplicated cysts; (2) cysts complicated by infection; (3) cysts complicated by cholangitis. Median postoperative stay for patients with uncomplicated cysts was 14 (range 6–50) days, while for those with complicated cysts this was 30 (range 9–109) days.

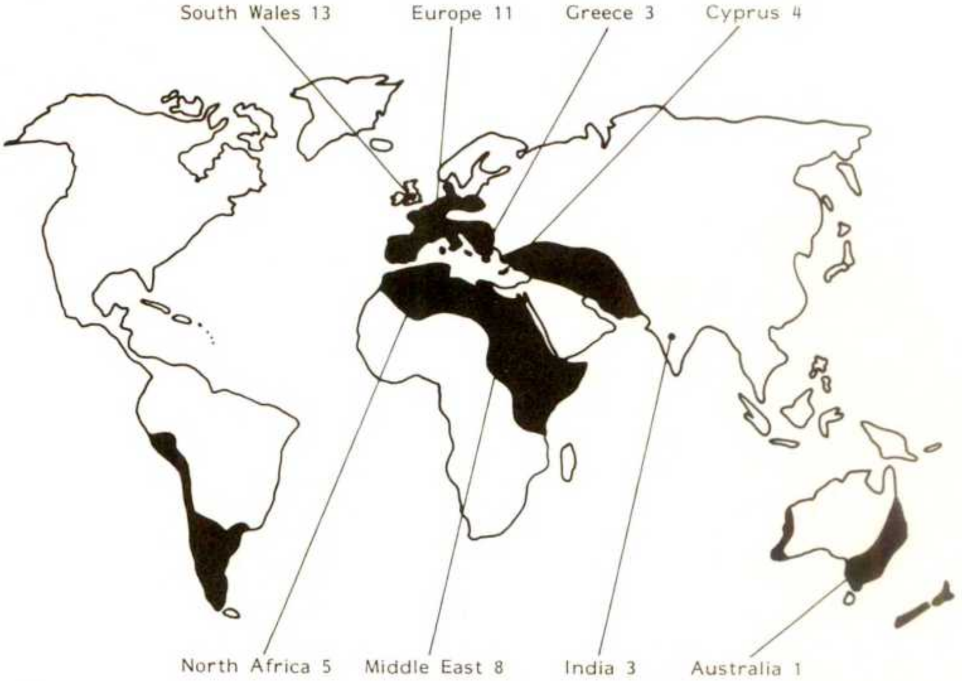


Figure 1 *Geographic origin of patients with hepatic hydatid disease in relation to hyperendemic areas of the world*[1]

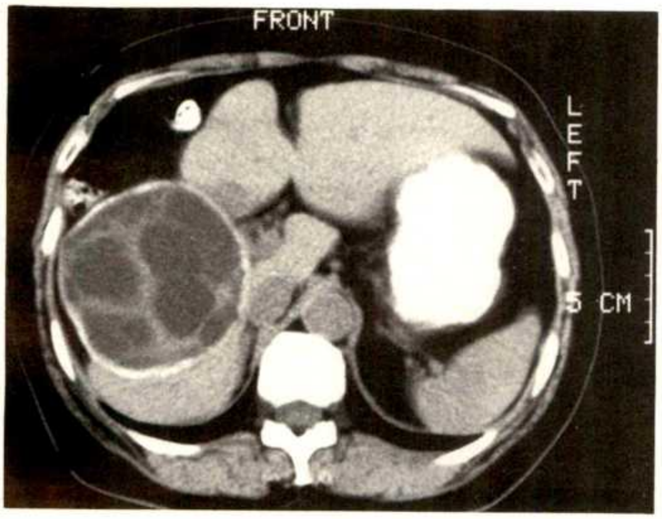


Figure 2 *Computerized tomographic scan of a patient with a large calcified hydatid cyst containing daughter cysts*

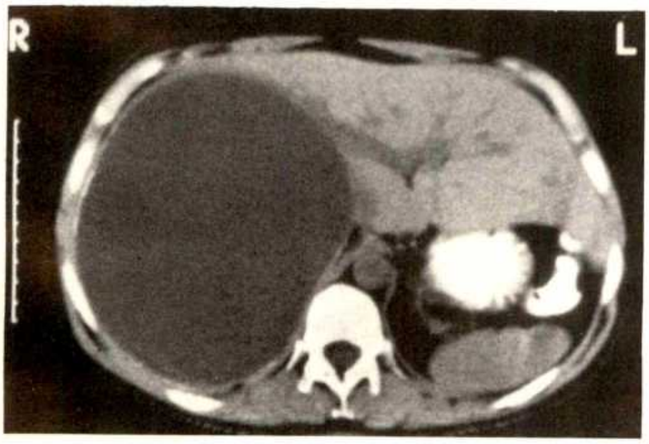


Figure 3 *A large suprarenal hydatid cyst misdiagnosed pre-operatively as an hepatic hydatid cyst*

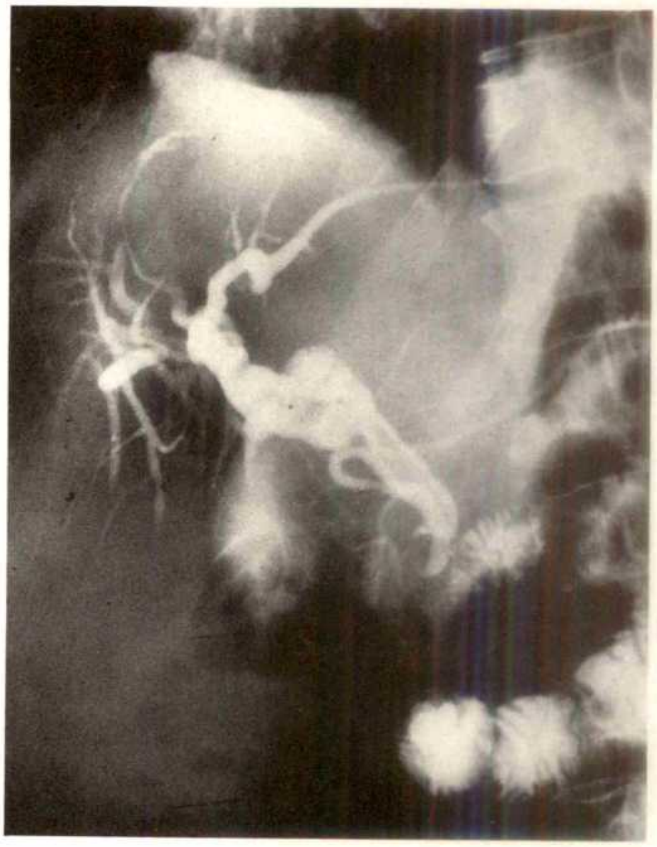


Figure 4 *Daughter cysts in the common bile duct demonstrated by pre-operative endoscopic retrograde cholangiopancreatography*

Uncomplicated cysts (Table 1)

In 26 of the 32 patients with uncomplicated cysts, omentoplasty was performed. In 21 there were no postoperative complications. Two developed significant bile leaks which closed spontaneously at 16 and 25 days respectively. One patient developed a staphylococcal infection following a sinogram on the tenth postoperative day, and this took almost a year to resolve. One

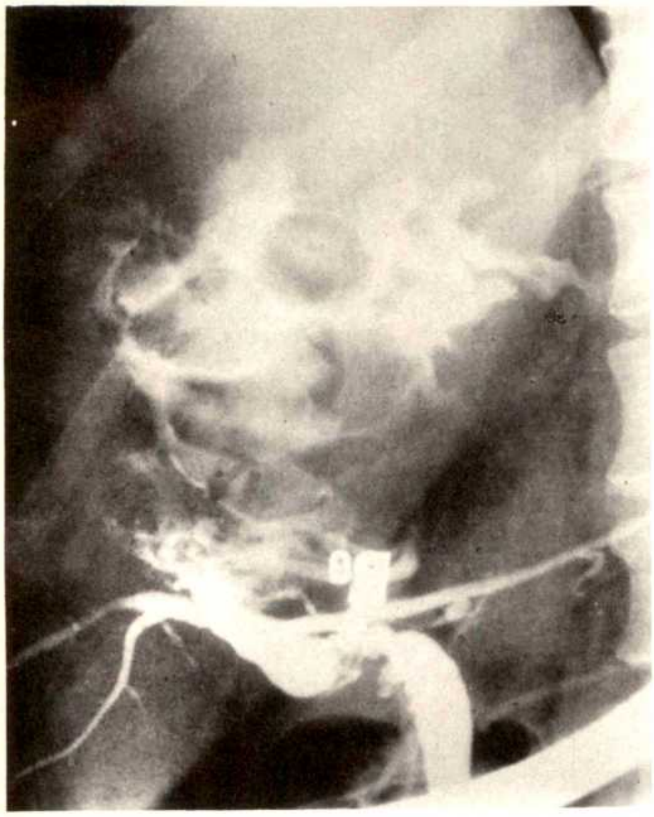


Figure 5 *Cholangiogram demonstrating communication between biliary tree and hydatid cyst with contained daughter cysts*

elderly woman who finally underwent surgery because of severe right hypochondrial pain was recovering uneventfully when she suddenly collapsed and died from a myocardial infarction 19 days postoperatively. Finally, a 60-year-old woman whose cyst was firmly adherent to her diaphragm required a diaphragmatic repair at the end of her operation, after which she developed a severe basal pneumonia requiring ventilation and tracheostomy before recovery and discharge home on the 50th postoperative day.

Four uncomplicated cysts were managed by drainage alone, either because no omentum was available (one case) or because the residual cavity was so shallow and draining dependently that omentoplasty was considered unnecessary. Two patients with almost complete cystic replacement of the left lobe were treated by left lateral segmentectomy.

To date, one patient with an uncomplicated cyst has developed a recurrence (over follow-up periods ranging from 2 months to 15 years). He was originally referred with a recurrent cyst which was treated by partial cystectomy and omentoplasty. Three years later he required surgery for a further cyst in the right lobe adjacent to his intact omental graft.

Infected cysts (Table 1)

In this group of patients omentoplasty was not possible because of previous surgery in three patients and a posterior approach in one patient: all four developed complications. In two patients, following evacuation of pus, daughter cysts and debris, prolonged tube drainage (84 and 120 days) was necessary before the cavity closed. The third patient, a 76-year-old woman, was referred after two previous operations for hepatic hydatid disease. Her right upper quadrant was a honeycomb of infected cysts and despite further drainage she gradually deteriorated and died. Post-mortem examination revealed anaplastic carcinoma in the wall of a cavity alongside the hyalinized remnant of a dead hydatid cyst. The remaining patient in this group presented with weight loss and an enlarging upper abdominal mass. At operation, a 4-litre heavily calcified cyst was found replacing the right lobe of the liver and connected to an epigastric mass which contained purulent fluid. The hepatic cyst was marsupialized to the abdominal wall and managed by repeated packing and gradual piecemeal resection of the calcified pericyst, allowing the cavity to collapse and the wound to heal.

Cysts associated with cholangitis (Table 2)

These patients typically presented with rigors, fever and jaundice. Careful radiological assessment of the biliary tree by ERCP or operative cholangiography was necessary. In one case, however, ERCP led to *Klebsiella* colonization of the biliary tree, with postoperative infection of a heavily calcified cavity, sloughing of the omental graft and a persistent biliary fistula. Control of the fistula was eventually obtained at a second operation by Roux loop drainage of the cyst cavity.

A 50-year-old man had no demonstrable intrahepatic cyst. Previous cholecystectomy and operative cholangiography were reported as normal but, after referral, exploration of the common bile duct revealed multiple daughter cysts and a choledochoduodenostomy was fashioned with a good result.

One patient in this group has required further surgery. She was initially referred with an infected recurrent hepatic hydatid cyst which was treated by drainage and omentoplasty. Four years later, she returned with recurrent cholangitis when daughter cysts were removed from the common bile duct and a cholecystectomy and sphincteroplasty were performed. Five years later, she developed a discharging wound sinus which was explored and found to relate to another cyst in the postero-inferior part of the right lobe (the previous omental graft appearing healthy). This was approached through a posterior 12th rib incision, infected material was evacuated and the cavity drained; since then she has remained well.

Discussion

Hydatid disease is rare in the UK, except for the southern part of Wales and Herefordshire[2]. The relatively high incidence of patients with complicated hydatid disease in this series reflects the referral pattern to a centre with a special interest in hepatobiliary disease.

Once considered, hepatic hydatid disease was not usually difficult to diagnose but two points are worth noting. Firstly, calcified cysts (25 per cent in this series) frequently contain live scolices[3] and calcification does not prevent pyogenic infection or cholangitis. Secondly, serology was negative in 20 per cent of the patients tested and may therefore be misleading. The sensitivity of the CFT has been reported to be 84 per cent with a specificity of 37 per cent, the corresponding figures for ELISA being 94 per cent and 65 per cent[4]. A recent review employing both tests revealed an overall false-negative rate of 15 per cent[5]. In the absence of characteristic radiological features such as daughter cysts on ultrasound/CT scanning (which may occur in one-third of patients[5]) and with hydatid disease wrongly excluded on the basis of negative serology, attempted percutaneous puncture of a cyst may result in anaphylaxis, urticaria and subsequent intraperitoneal dissemination.

Table 1 *Surgical management of hepatic hydatid disease*

Presentation	Residual cavity		Complication	
Uncomplicated ($n = 32$)	Omentoplasty	26	None	27
	Tube drainage	4	Bile leak	2
	Left lateral segmentectomy	2	Secondary sepsis	1
			Pneumonia	1
			Death (myocardial infarction)	1
Complicated (pyogenic infection) ($n = 4$)	Tube drainage	4*	Prolonged drainage	3
			Death (sepsis + carcinoma)	1

* No omentum available

Table 2 *Management of hepatic hydatid disease in patients presenting with cholangitis*

Patient no	Biliary tract	Associated problems	Treatment	Complications
1	Normal	Cholangitis	Omentoplasty	None
2	Normal	Cholangitis	Omentoplasty ECBD/cholecystectomy	None
3	Normal	Cholangitis	Omentoplasty	None
4	Normal	Cholangitis Infected cyst	Left lateral segmentectomy Cholecystectomy	None
5	Daughter cysts	Cholangitis	Omentoplasty ECBD/cholecystectomy Sphincteroplasty	None
6	Daughter cysts	Cholangitis	ECBD/choledochoduodenostomy	None
7	Daughter cysts	Cholangitis	Omentoplasty ECBD/cholecystectomy	None
8	Extrinsic obstruction by infected cyst	Cholangitis Subhepatic abscess	Drainage only	None
9	Extrinsic obstruction by hilar cyst	Cholangitis	Omentoplasty	Wound sepsis
10	Daughter cysts	(a) Infected recurrent cyst (b) Cholangitis	(a) Omentoplasty (b) ECBD/cholecystectomy and sphincteroplasty	Recurrent cyst (see text)
11	Daughter cysts	Cholangitis Deep jaundice Portal hypertension	Drainage Sphincterotomy	Hepatobronchial fistula
12	Extrinsic compression by cyst	Cholangitis Heavily calcified cyst	Omentoplasty Cholecystostomy	Infected cavity Biliary fistula (see text)

ECBD, exploration of common bile duct

There is debate not only as to the most effective scolicide but also about the value of scolicidal injection before cyst evacuation[6]. Perhaps the most important aspect of this manoeuvre is partial decompression of the cyst contents which are under tension. The use of scolicidal agents has a long tradition but there is little evidence to justify their use and they are probably of negligible value in multivesicular cysts. In an attempt to obviate the need for initial injection of scolicide, Saidi has developed a cryogenic cone to obtain entry to and evacuation of the cyst without fear of spillage into the peritoneal cavity[7]. We have no experience of this method (or of the suction cone devised by Aarons and Kune[8]). However, the bulk of the cone demands a wide exposure which for the common superior cyst of the right lobe entails a thoraco-abdominal approach (K. Hobbs, personal communication). One patient in our series was referred after earlier surgery using this technique and was noted to have skin burns from the device. Furthermore, as the cyst collapses adherence of the cone to the cyst wall may be lost

We have used a variety of scolicidal agents (2 per cent formalin, 0·5 per cent silver nitrate and 10 per cent aqueous povidone iodine) without any obvious deleterious effects. However, both formalin and hypertonic saline may be associated with acute toxicity[9,10] and there is evidence that spillover of either agent into the biliary tree can lead to a sclerosing cholangitis[11]. We have observed this in a patient referred after the use of silver nitrate solution. Intracystic injection of scolicide should not be used if preliminary aspiration yields bile-stained fluid or if there is radiological or clinical evidence to suggest a biliary communication.

Further developments with the benzimidazole compounds may make scolicidal agents obsolete as sterilization of the cyst contents by pre-operative chemotherapy[12] and adequate perioperative blood levels should eliminate the risk of intra-operative dissemination and recurrent disease.

A wide variety of techniques has been recommended to deal with the rigid cavity created by the pericyst Practised alternatives include: hepatic resection[13,14]; pericystectomy[15,16]; partial cystectomy combined with omentoplasty[17–19], suture obliteration (capitonnage)[20], cystojejunostomy[21], marsupialization[22] or external drainage[23] and finally primary closure after saline instillation[24].

Whenever possible, we managed the residual cyst cavity by omentoplasty. This technique has been shown to reduce hospital stay and lower the incidence of biliary fistula compared with marsupialization or tube drainage[17]. Our findings confirm these satisfactory results. Omentoplasty was performed in 34 of 44 patients with a residual intrahepatic cavity. The median postoperative stay (12 days, range 6–50) contrasts sharply with that of 10 patients in whom the technique was not employed (21 days, range 8–109). In this latter group, three patients had very shallow residual cavities draining dependently and omentoplasty was considered unnecessary; their postoperative courses were uneventful. However, in the other seven patients, omentum was not available because of previous surgery (six cases) and a posterior approach (one case) and six suffered prolonged postoperative courses due in part to their complex disease and in part to a persistent infected cavity Nevertheless, two patients in the omentoplasty groups developed septic complications, one following a sinogram and the other after an ERCP (see above).

Intrabiliary rupture is the commonest complication of hepatic hydatid cysts[25,26]. Twelve patients in this series (25 per cent) had cysts associated with cholangitis. The principles of operative management in these cases were to treat the mother cyst and to clear the biliary tree of any hydatid material Biliary communications with the mother cyst close spontaneously after operation provided adequate external drainage exists and cholangiography has excluded distal biliary obstruction from cyst debris, daughter cysts or coincidental gallstones. Thus it is essential to obtain satisfactory cholangiograms and, where indicated, to proceed with cholecystectomy and exploration of the common bile duct A drainage procedure or an endoscopic sphincterotomy[27] should be added if there is any doubt about free biliary drainage.

In conclusion, our experience confirms that uncomplicated cases of hepatic hydatid disease can be managed successfully by conservative surgery and the results obtained do not support the more widespread use of hepatic resection or pericystectomy advocated by others. Important points in the management of these patients are adequate radiological assessment of the biliary tree in those with a history of jaundice or cholangitis or in the presence of bile-stained cyst contents, careful isolation

LIBRARY

of the cyst at operation and the management of the residual cavity by omentoplasty whenever possible.

Acknowledgements

We wish to thank Dr H. Nunnerly and Dr J. W. Laws for their radiological expertise and advice and Mr B. Pike and Ms L. Wilson for photographic work.

References

1 Gemmell MA. Hydatidosis control—a global view. *Aust Vet J* 1979; **55**: 118–25.
2. Stallbaumer MF, Clarkson MJ, Bailey JW, Pritchard JE. The epidemiology of hydatid disease in England and Wales. *J Hyg Camb* 1986; **96**: 121–7.
3. Beggs I. The radiological appearances of hydatid disease of the liver. *Clin Radiol* 1983, **34**: 555–63.
4. Stallbaumer MF, Clarkson JM, Pritchard JF, Bailey JW, Morris DL. Serological diagnosis and current epidemiology of hydatid disease in England and Wales. *Gut* 1983; **24**: A996.
5. Harris KM, Morris DL, Tudor R, Toghill P, Hardcastle JD. Clinical and radiographic features of simple and hydatid cysts of the liver. *Br J Surg* 1986; **73**: 835–8
6. Saidi F. *Surgery of Hydatid Disease*. London. WB Saunders, 1976.
7. Saidi F. A new approach to the surgical treatment of hydatid cysts. *Ann R Coll Surg Engl* 1977; **59**: 115–28.
8. Aarons BJ, Kune GA. A suction cone to prevent spillage during hydatid surgery. *Aust NZ J Surg* 1983; **53**. 471–4.
9 Aggerwal AR, Garg RL. Formalin toxicity in hydatid liver disease. *Anaesthesia* 1983; **38**: 662–5
10. Wanninayake HM, Brough W, Bullock N, Calne RY, Farman JV. Hypernatraemia after treatment of hydatid. *Br Med J* 1982; **284**: 1302–3.
11 Belghiti J, Benhamou J, Houry S, Grenier P, Huguier M, Fekete F. Caustic sclerosing cholangitis. *Arch Surg* 1986; **121**: 1162–5.
12. Morris DL. Pre-operative albendazole therapy for hydatid cyst. *Br J Surg* 1987; **74**: 805–6
13. Belli L, Favero E, Marni A, Romani F. Resection versus pericystectomy in the treatment of hydatidosis of the liver. *Am J Surg* 1983; **145**. 239–42
14. Pissiotis CA, Wander JU, Condon RE. Surgical treatment of hydatid disease. Prevention of complications and recurrence. *Arch Surg* 1972; **104**: 454–9.
15. Placer-Galan C, Martin R, Jimenez R, Soleto E. A simplified technique for surgical management of echinococcal cyst. *Surg Gynecol Obstet* 1987, **165**: 269–70
16. Belli L, Romani F, Puttini M. Easier and safer cystopericystectomy using the Pringle manoeuver. *Surg Gynecol Obstet* 1987, **164**: 75–6.
17. Papadimitriou J, Mandrekas A. The surgical treatment of hydatid disease of the liver. *Br J Surg* 1970; **57**. 431–3.
18. Little JM, Deane SA. Hydatid disease. In: Bengmark S, Blumgart LH, eds. *Liver Surgery*. Edinburgh: Churchill Livingstone, 1986: 118–29.
19. Kune GA. Hydatid disease. In: Schwartz SI, Ellis H, eds. *Maingot's Abdominal Operations*. 8th ed. Connecticut: Appleton-Century-Crofts, 1985 1605–24.
20. Akinoglu A, Bilgin I, Erkocak EU. Surgical management of hydatid disease of the liver. *Can J Surg* 1985; **28**: 171–4.
21 Sekar N, Mahajan KK, Kaushik SP, Katariya RN. Pericystojejunostomy in the treatment of hydatid cysts of the liver. *Aust NZ J Surg* 1982; **52**: 76–8.
22. Romero-Torres R, Campbell JR. An interpretive review of the surgical treatment of hydatid disease. *Surg Gynecol Obstet* 1965; **121**: 851–64
23. Barros JL. Hydatid disease of the liver. *Am J Surg* 1978; **135**: 597–600.
24. Ekrami Y. Surgical treatment of hydatid disease of the liver. *Arch Surg* 1976; **111**: 1350–2.
25. Dew HR. *Hydatid Disease*. Sydney: The Australasian Medical Publishing Company Limited, 1928.
26 Androulakis GA. Surgical management of complicated hydatid cysts of the liver. *Eur Surg Res* 1986; **18**: 145–50.
27. Ponchon T, Bory R, Chavaillon A. Endoscopic retrograde cholangiography and sphincterotomy for complicated hepatic hydatid cyst. *Endoscopy* 1987; **19**: 174–7.

Br. J. Surg. 1988, Vol. 75, October,
951–953

Cholecystokinin (CCK) provocation test: long-term follow-up after cholecystectomy

**M. Rhodes,
T. W. J. Lennard,
J. R. Farndon and
R. M. R. Taylor**

*University Department of Surgery,
New Medical School,
Framlington Place, Newcastle upon
Tyne NE2 4HH, UK*
Correspondence to:
Mr T. W. J. Lennard

Over a 6-year period 264 cholecystokinin (CCK) provocation tests have been performed in 174 patients with undiagnosed right upper quadrant pain. All were carried out by one person (T.W.J.L.) as part of a prospective placebo-controlled crossover study. Following infusion of CCK but not saline, 103 patients developed pain (CCK + ve). These patients were offered cholecystectomy and 90 accepted. Seventy patients developed no pain during either infusion (CCK − ve), and one patient experienced pain with both CCK and saline infusions. Of the 90 patients who underwent cholecystectomy, 81 (90 per cent) have been followed up for a mean of 35 months (range 12 months to $5\frac{1}{2}$ years), 67 per cent have had complete resolution of symptoms and a further 24 per cent have had a marked improvement in symptoms. Only 9 per cent of patients did not benefit from cholecystectomy. This compares well with patients undergoing cholecystectomy for uncomplicated calculous gallbladder disease, 88 per cent of whom, in our study, were improved by surgery. Patients with a positive CCK test have an excellent chance of symptomatic improvement following cholecystectomy.

Keywords: Acalculous biliary pain, cholecystokinin provocation test, cholecystectomy

Patients who have symptoms that are clinically suggestive of gallstones but who do not have demonstrable biliary disease on oral cholecystography or upper abdominal ultrasound can be a diagnostic problem. We have previously described the use of the cholecystokinin (CCK) provocation test in these patients[1]: those with a positive response to intravenous CCK but not to placebo (CCK + ve) did very well after cholecystectomy. This report examines the long-term results of cholecystectomy in CCK + ve patients and reviews over 6 years' experience with this test.

Patients and methods

Over a 6-year period 174 patients were referred for a CCK test (*Table 1*) because of unexplained right upper quadrant pain. All patients had normal oral cholecystography, abdominal ultrasonography and upper gastrointestinal endoscopy on at least one occasion. Mean symptom duration before referral for the CCK test was 40 months (range 2–240 months), probably reflecting the difficulty in achieving a diagnosis in these patients CCK tests were carried out by a single operator (T.W.J.L.) as previously described[1]. Briefly, CCK (KabiVitrum, Nykoping, Sweden) was administered as a slow intravenous injection over 5 min in a dose of 1 Ivy dog unit/kilogram body weight. Placebo infusion was normal saline. CCK and placebo were administered in a double-blind, crossover fashion. All patients who developed pain during the CCK infusion were offered cholecystectomy and 90 of the 103 CCK + ve patients underwent this operation. Six weeks after operation CCK and placebo infusions were repeated in an identical fashion Over the same time period 130 patients underwent cholecystectomy for uncomplicated gallstones (*Table 1*). Long-term follow-up of patients after cholecystectomy was carried out by a standard questionnaire for all patients. Patients with no symptoms were classified as cured, those with minor symptoms only as improved and those unchanged or worse after surgery as failures. Patients who developed no pain with either infusion or pain with both (CCK −ve) were followed up and investigated as required by the referring surgical unit. Histopathology of resected gallbladders was reported by independent pathologists who were unaware of the study.

Results

A total of 103 patients developed their usual symptom pain in response to the CCK infusion but not to the placebo (CCK + ve) and 70 patients developed no pain with either infusion (CCK − ve). One patient developed pain with both infusions (scored as CCK − ve). Follow-up has been achieved in 81 of the 90 (90 per cent) patients undergoing cholecystectomy and 9 were lost to follow-up (1 patient died from breast carcinoma and 8 patients left the area). Mean follow-up duration was 35 months (range 12–66). Of those who underwent cholecystectomy 67 per cent were completely satisfied and cured of all pain. A further 24 per cent were improved by the operation but had minor occasional discomfort which did not significantly affect their lifestyle. Only 9 per cent of patients did not feel they had benefited from cholecystectomy. No patient developed pain during postoperative CCK tests.

The follow-up of 130 patients (using the same questionnaire) undergoing cholecystectomy for uncomplicated calculous gallbladder disease in the Newcastle teaching hospitals yielded 106 replies (81 per cent). Two patients died (carcinoma of the lung and myocardial infarction) and 22 were lost to follow-up. Of the 106 responders, 65 (61 per cent) had complete relief of symptoms while a further 28 (26 per cent) were partially improved. There were 13 (12 per cent) in whom no change or a worsening of symptoms occurred. None of these patients was jaundiced or had an abnormal peroperative cholangiogram.

In acalculous disease 80 of the 81 gallbladders removed were available for histological analysis: 52 showed chronic cholecystitis, 23 no abnormality and 2 cholesterolosis. A single gallbladder showed adenomatous hyperplasia and two showed simple muscle hypertrophy.

Table 1 *Mean age, symptom duration and sex characteristics of referred patients*

	CCK +ve	CCK −ve	Gallstones*
Male	15	19	25
Female	88	52	81
Symptoms (months)	50	30	4
Age (years)	44	43·6	53
Satisfied after operation (%)	91	—	88

CCK +ve, a positive pain response to intravenous cholecystokinin infusion and not to placebo; CCK −ve, a negative pain response to either infusion, or pain with both, *24 gallstone patients were lost to follow-up

Table 2 *Proportion of histopathologically abnormal gallbladders after cholecystectomy for positive response to cholecystokinin provocation test*

Series	Reference	% Abnormal
Lennard *et al.*	1	71
Burnstein *et al*	11	95
Valberg *et al.*	12	66
Gunn *et al*	8	60
Nathan *et al.*	13	100
Reid *et al*	15	50
Sykes	4	75
Nora *et al.*	16	100

Discussion

Investigations used to help diagnose unexplained right upper quadrant pain have included CCK cholecystography[2], bile analysis[3], CCK provocation tests[1,4,5] and distension of the colon[6]. Many of these studies have no control arm and are difficult to interpret[2]. 'Blind' cholecystectomy for right upper quadrant pain of unknown aetiology provides symptomatic relief in 30 per cent[7] to 75 per cent of patients[8].

The results of this study demonstrate that cholecystectomy in CCK + ve patients compares favourably with cholecystectomy for uncomplicated calculous gallbladder disease. Thirteen CCK + ve patients did not undergo cholecystectomy. These patients were either unfit for surgery or moved away from the northern region, and long-term follow-up in this important group has been impossible in most cases

We have felt that the significance of a negative response to CCK remains entirely open and early follow-up of 59 CCK − ve patients[9] revealed that 25 per cent remained without a diagnosis, 15 per cent improved spontaneously and 60 per cent were assigned a new diagnosis, supporting our view that CCK − ve patients do not have biliary disease and will not benefit from cholecystectomy.

Debate has centred on whether CCK should be given as a bolus or an infusion[10] but the rate of gallbladder emptying is similar during the first 25 min of CCK administration. Combining the analysis of duodenal bile with CCK tests had been advocated[3], but false negative results can occur if the cystic duct is blocked or the gallbladder can only contract poorly in response to CCK. Particle formation within bile can occur if it is exposed to a low pH giving a false positive result. Freeman *et al.*, using pain reproduction, cholangiography and duodenal bile analysis[3], achieved 'no therapeutic failures' in 22 patients undergoing cholecystectomy for right upper quadrant pain.

Two patients had undergone previous laparotomy for their pain, but had no symptomatic relief until the gallbladder was removed at the second operation. CCK cholecystography, bile analysis and pain reproduction during CCK infusions resulted in symptomatic improvement in all 21 patients selected for cholecystectomy in the series of Burnstein *et al.*[11]. Patients in this study who declined surgery continued to have pain and a highly selected group of patients (9 out of 42) with a negative test but continuing pain did undergo cholecystectomy, with 8 of them showing improvement. Valberg *et al.*[12] reported 12 patients who developed pain after CCK infusion and underwent cholecystectomy—all with symptom cure. Only 2 of the 12 patients had postoperative CCK infusions and they developed no pain during these. Using CCK cholecystography and pain reproduction, Nathan *et al.*[13] reported that all 49 patients undergoing cholecystectomy for a positive test were cured, and Goldstein *et al.*[14] reported similar results in their series of 25 patients. Sykes[4] reported 15 patients who were operated upon on the basis of pain reproduction by CCK, 14 of whom were cured by cholecystectomy. Reid *et al.*[15] reported equally good results in CCK + ve ($n = 4$) and CCK − ve ($n = 5$) patients, but 2 of the CCK − ve patients did have gallstones. Using CCK cholecystography, Nora *et al.*[16] have achieved 80 per cent cure in their CCK + ve patients (up to 6 years follow-up in some). Of the 76 patients in their series with abnormal gallbladder emptying, only 30 underwent surgery and it is not clear how these were selected—they were all cured at follow-up from 1 to 3½ years, but 10 of them had calculi when the gallbladder was opened.

The incidence of pathological abnormality in resected gallbladders after CCK + ve tests varies (*Table 2*) and does not relate to clinical outcome.

If chronic cholecystitis or cholesterolosis alone are not the causes of acalculous biliary pain, then tension within the gallbladder owing to a blocked cystic duct or mild cholecystitis which subsequently resolves may cause pain.

A decrease in CCK receptors in the gallbladder may be an early event in the pathogenesis of gallstone formation by causing defective gallbladder motility[17]. Cholesterolosis too has been recently re-implicated as a cause of right upper quadrant pain[18]. Nora *et al.*[16] have suggested that patients with acalculous biliary pain 'may be predisposed to eventual cholesterol gallstone formation'. If true, gallbladder disease may be identified before stones develop, the complications of gallstones avoided, and surgery should be safer in fitter, younger, patients. Our results confirm the usefulness of the placebo-controlled CCK provocation test. If positive the patient can be advised that he or she will have as good a chance of symptom cure following cholecystectomy as someone with gallstones[19,20]. We agree with Burnstein *et al.*[11] that 'in one centre, the CCK test is probably best done by one interested individual' Our data do not support the recent suggestion[21] that there is 'no place for the use of CCK in the management of patients' thought to have acalculous biliary pain'.

Acknowledgements

The authors are grateful to all the surgeons in the Northern Region who have allowed their patients to be studied, and to Mrs Margaret Canham for typing the manuscript.

References

1. Lennard TWJ, Farndon JR, Taylor RMR. Acalculous biliary pain. diagnosis and selection for cholecystectomy using the cholecystokinin test for pain reproduction *Br J Surg* 1984, **71**· 368–70.
2. Dunn FH, Christensen EC, Reynolds J *et al* Cholecystokinin cholecystography *JAMA* 1974; **228**· 997, 1003.
3. Freeman JB, Cohen WN, DenBesten L. Cholecystokinin cholangiography and analysis of duodenal bile in the investigation of pain in the right upper quadrant of the abdomen without gallstones *Surg Gynecol Obstet* 1975, **140** 371–6.
4. Sykes D. The use of cholecystokinin in diagnosing biliary pain. *Ann R Coll Surg Engl* 1982, **64**: 114–16.
5. Cozzolino HJ, Goldstein F, Greening RR *et al.* The cystic duct syndrome *JAMA* 1963; **185**. 920–4.
6. Kingham JGC, Dawson AM Origin of chronic right upper quadrant pain. *Gut* 1985; **26**: 783–8.
7. Mackey WA Cholecystitis without stones. *Br J Surg* 1934, **22**: 274–95.
8. Gunn A, Keddie NC, Fox H. Acalculous gallbladder disease *Br J Surg* 1973, **60**: 213–15.
9. Lennard TWJ, Farndon JR, Taylor RMR. The cholecystokinin provocation test in suspected acalculous biliary pain Three and a half years of clinical use. *Gut* 1985, **26**: 1158.
10. Hopman WPM, Jansen JBMJ, Rosenbursch G, Lamers CBHW. Gallbladder contraction induced by cholecystokinin bolus injection or infusion? *Br Med J* 1986; **292**: 375–6.
11. Burnstein MJ, Vassal KP, Strasberg SM. Results of combined biliary drainage and cholecystokinin cholecystography in 81 patients with normal oral cholecystograms. *Ann Surg* 1982; **196**. 627–32.
12. Valberg LS, Jabbari M, Kerr JW *et al.* Biliary pain in young women in the absence of gallstones. *Gastroenterology* 1971, **60**: 1020–6
13. Nathan MH, Newman A, MacFarland J, Murray DJ. Cholecystokinin cholecystography *Radiology* 1969; **92**· 1–8.
14. Goldstein F, Gaunt RF, Margulies M Cholecystokinin cholecystography in differential diagnosis of acalculous gallbladder disease. *Gastroenterology* 1972; **62**· 756

15 Reid DRK, Rogers IM, Calder JF. The cholecystokinin test: an assessment *Br J Surg* 1975, **62**: 317–19.
16. Nora PF, Davis P, Fernandez MJ Chronic acalculous gallbladder disease: a clinical enigma. *World J Surg* 1984; **8**· 106–12.
17. Upp, JR, Nealon WH, Singh P *et al.* Correlation of cholecystokinin receptors with gallbladder contractility in patients with gallstones *Ann Surg* 1987; **205**: 641–7
18. Jacyna MR, Bouchier IAD. Cholesterolosis· a physical cause of 'functional' disorder. *Br Med J* 1987; **295**: 619–20
19. Bodvall B. The postcholecystectomy syndromes *Clin Gastroenterol* 1972, **2**· 103–26.
20. Ros E, Zambon D. Postcholecystectomy symptoms. A prospective study of gallstone patients before and 2 years after surgery. *Gut* 1987; **28**: 1500–4.
21. Sunderland GT, Carter DC. Clinical application of the cholecystokinin provocation test *Br J Surg* 1988, **75** 444–9.

Report of the visit of the Association of Surgeons of Great Britain and Ireland to Australia

A party of Fellows of the Association of Surgeons of Great Britain and Ireland, together with their wives and under the leadership of our President, Mr Norman Addison, visited Sydney to attend the 32nd World Congress of Surgery in September 1987. The Cardiovascular Society also met in Sydney the same week. The meeting was extremely well organized and provided a feast of papers. In addition, there was an excellent programme of films, posters and lunchtime seminars. Sydney was a wonderful venue and the weather was perfect. The opening ceremony took place in the Sydney Opera House followed by a reception and was graced by a local physician who is a superb organist and entertained us at the ceremony. The 'accompanying persons' programme was well organized and there were social events in the evening, culminating in the farewell banquet at the Sheraton Wentworth Hotel. The organizers are to be congratulated, especially Dr Alistair Brown who was Chairman of the local organizing committee.

The party next moved to Melbourne and had a half day meeting at the Australasian College of Surgeons. This is a beautiful building, superbly situated in the centre of Melbourne. The programme consisted of a variety of papers presented by Fellows of the Association; the first session was chaired by the President of the Royal Australasian College, Mr E. Durham Smith, and the second session was chaired by Norman Addison.

The final presentation was by D. G. Macleish, immediate past President of the Royal Australasian College. He gave us a fascinating account of the development of the College. It was of particular interest to the Fellows of the Association that Professor Wood Jones and Sir Gordon Gordon-Taylor held a special place in the annals of the College. Their portraits were both prominently placed as was that of Sir Gordon Gordon-Taylor's wife. Another portrait of interest to the British contingent was that of Professor Grey-Turner. In the evening we had a joint dinner in the Melbourne Cricket Ground when we were privileged to see the library and museum of the Club as well as the President's inner sanctum. A fascinating feature of this was the President's private facilities which allowed viewing of the pitch while passing his water!

The party then moved on to Brisbane where a further scientific session was held in conjunction with the local Fellows of the Royal Australasian College at the Mater Misericordiae Hospital; papers were presented by Fellows of the Association and Fellows of the Royal Australasian College. In the evening, an excellent dinner was held with our hosts at the United Services Club. From Brisbane, most of the party proceeded to the Great Barrier Reef.

This visit has proved to be extremely successful scientifically and socially. Friendships were made and contacts renewed. Norman Addison is to be congratulated on conceiving and organizing this visit. Thanks are also due to Barry Jackson our patient Secretary and Roger Baird our Treasurer.

N. Keddie

Br. J. Surg. 1988, Vol. 75, October, 954–960

ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis

A total of 131 patients with acute pancreatitis (of whom 100 had gallstones) underwent endoscopic retrograde cholangiopancreatography (ERCP) during the same hospital admission. Urgent ERCP (<72 h) was performed in 68 cases and early ERCP (3–30 days) in 63 cases; 47 had predicted severe attacks and 84 had predicted mild attacks (modified Glasgow criteria). The highest incidence of common bile duct stones occurred in those with predicted severe attacks and those who had urgent ERCP. Highly significant correlations were found between age and common bile duct and pancreatic duct diameters. Significant correlations were also found between the common bile duct and pancreatic duct (correcting for age) and between these and the admission serum bilirubin. The common bile duct diameter was greatest in those with common bile duct stones and predicted severe attacks. A considerably lower incidence of pancreatic duct filling occurred in those with predicted severe attacks and common bile duct stones; in predicted mild attacks the pancreatic duct diameter was greater in those with common bile duct stones. In gallstone patients complications were highest in those with predicted severe attacks but more significantly in those with common bile duct stones. Endoscopic sphincterotomy was undertaken in 37 patients with common bile duct stones without mortality. The overall complication rate in gallstone patients was 19 per cent and the mortality rate was 2 per cent. These findings suggest that common bile duct stones cause acute common bile duct and pancreatic duct obstruction and are closely associated with complications. Urgent ERCP for detection of common bile duct stones, and endoscopic sphincterotomy for treatment, is strongly recommended for patients with predicted severe attacks due to gallstones and should also be considered for others who fail to show clinical improvement.

Keywords: Acute pancreatitis, gallstones, endoscopic retrograde cholangiopancreatography, common bile duct, pancreatic duct, pancreas divisum

J. P. Neoptolemos,
D. L. Carr-Locke*,
N. London,
I. Bailey and
D. P. Fossard

*Departments of Surgery and *Gastroenterology, The Leicester Royal Infirmary, Leicester General Hospital and Glenfield General Hospital, Leicester, UK*

Correspondence to:
Mr J. P. Neoptolemos,
University Department of Surgery,
Dudley Road Hospital,
Birmingham B18 7QH, UK

In 1925 Moynihan wrote: 'There can be no doubt that recovery from acute pancreatitis of all grades, except the most severe, is possible without operation... It is, however, equally certain that recovery from the disease, apart from operation, is so rare that no case should be left untreated.' Both Moynihan[1] and Mayo[2] stressed the importance of urgent biliary drainage in the presence of gallstones. Apparent deficiencies in the common channel theory[3], as proposed by Opie[4], as well as great improvements in supportive care[5] fuelled a controversy between urgent biliary decompression and conservative management which to a greater or lesser extent remains unresolved.

The finding that virtually all patients with gallstone associated pancreatitis pass gallstones through the ampulla of Vater[6–8] has been interpreted by some as a basis for recommending urgent surgery[9–12] and by others as a reason for avoiding it[13–17]. This has also led to the idea that bile reflux into the pancreatic duct results from oedema of the ampulla of Vater caused by the migrating gallstones rather than by an impacted gallstone, as proposed by Opie[4]. An alternative explanation is that the migrating gallstones result in a gaping ampulla of Vater thereby promoting reflux of activated duodenal enzymes into the pancreatic duct[18]. Thus, although there appears to be general agreement that common bile duct stones are important in initiating the attack of acute pancreatitis, it is not known (a) whether they cause an acute obstruction to the common bile duct, pancreatic duct or both, and (b) whether their continued presence has any bearing on outcome.

The present study involved the systematic use of prognostic criteria of severity[19,20] and endoscopic retrograde cholangiopancreatography (ERCP) during the attack of acute pancreatitis in order to gain a further insight into these questions.

Patients and methods

One hundred and thirty-one patients with acute pancreatitis who underwent ERCP during the same hospital admission over a 10-year period form the main group of patients in this study. Fifty-nine of these patients were part of a prospective randomized trial of ERCP in patients with acute pancreatitis suspected to be due to gallstones[21]. Thirty-five additional patients with acute pancreatitis who underwent ERCP at between 1 and 6 months after the attack are included in certain aspects of the analysis.

The diagnosis of acute pancreatitis was based on a serum amylase >1000 units/l (Phadebas) in the presence of a compatible clinical picture (normal range of amylase <300 units/l). Patients with hyperlipidaemia and pseudohyponatraemia with a serum amylase of 900–1000 units/l were also included[22]

The predicted severity of the attack was determined using eight of the Glasgow criteria, including age >55 years, but excluding a serum alanine transaminase >200 units/l[19,20]. In addition, the serum bilirubin was measured within 48 h of admission, using the SMAC auto-analyser (Technicon, Tarrytown, USA) (normal range of bilirubin 3–17 μmol/l).

All patients had IV crystalloid and/or colloid, oxygen by mask or assisted ventilation as required to maintain adequate oxygenation and, in the case of patients with suspected gallstones, IV antibiotics for at least 3 days. All patients had at least one, and usually several, ultrasound examinations of the pancreas In the second half of the study period, patients who had urgent or early ERCP also underwent serial assessment of the pancreas by CT scanning including the use of IV contrast with at least the first of the scans (52 patients).

ERCP was performed using a standard technique as previously described[23] involving pharyngeal local anaesthesia (1 per cent lignocaine spray), mild sedation (diazepam 5–10 mg IV initially and in subsequent years midazolam 2·5–5 mg IV), and duodenal relaxation with hyoscine butyl bromide Undue manipulation of the ampulla of Vater was avoided No attempt was made to fill the pancreatic duct if ERCP was performed during the same hospital admission If there was successful cannulation of the common bile duct, the biliary tree was filled with contrast. If stones in the main bile ducts were detected, further contrast was not specifically given in order to fill the gallbladder if this had not already occurred. Complete filling of the biliary tree and pancreatic duct was attempted only in patients who had an ERCP after hospital discharge.

The terms urgent ERCP, early ERCP and delayed ERCP are used to describe the investigation performed at <72 h, 3–30 days and at 1–6 months respectively from the first day of the attack.

An endoscopic sphincterotomy was performed at the same time as ERCP only if bile duct stones were detected. A positive stone extraction policy was pursued, using previously described techniques[23]

The maximum diameter of the common bile duct and pancreatic duct were recorded prospectively at the time of ERCP, correcting for radiological magnification[24]. The presence of gallbladder filling by contrast and the presence of pancreas divisum were also recorded.

The diagnosis of gallstones was based on the finding of gallstones at laparotomy or post mortem or the unequivocal findings at ultrasonography or ERCP. The absence of gallstones was based on at least three ultrasound examinations and one ERCP, the findings at laparotomy including adequate cholangiography or the findings at post-mortem examination

Statistical analysis

All the data were recorded on a mainframe computer (University of Birmingham). Discrete variables were analysed using the χ^2 test, Yates' correction was used for small expected numbers Continuous variables were analysed using the two-tailed Mann–Whitney *U* test and analysis of covariance. Simple correlation coefficients (as well as the aforementioned tests) were determined using the Minitab computer package. Partial correlation coefficients were determined as described[25]

Significance was assumed when $P < 0{\cdot}05$; marginally significant values of $P = 0{\cdot}05–0{\cdot}1$ are also mentioned.

Results

Of the 131 patients who had ERCP during the same hospital admission, 100 were found to have gallstones. In 17 other patients no cause for the attack could be found (idiopathic group). Of the remaining 14 patients, the attack was associated with excess alcohol ingestion in 10 cases, two had hyperlipidaemia, one had polyarteritis nodosa and one had hypercalcaemia associated with parathyroidectomy (alcoholic/other group). Of the 35 patients who had a delayed ERCP, 16 had gallstones, 7 had idiopathic disease, and 12 had an alcohol history.

Details of sex, age and admission serum amylase in relation to predicted severity and timing of ERCP in all of these 166 patients are shown in *Table 1*. The incidences of filling of the biliary and pancreatic duct systems in these patients at ERCP are shown in *Table 2*. There were no significant differences between any of the subgroups with respect to successful cholangiography; in contrast, the pancreatic system filled significantly less often in those with gallstones and a predicted severe attack ($\chi^2 = 7{\cdot}10$, d.f. $= 1$, $P = 0{\cdot}0078$) *Table 3* shows the incidence of gallbladder filling during successful cholangiography; none of the differences was significant The incidence of common bile duct stones as determined from successful cholangiography, was higher in those with predicted severe attacks (*Table 4*); the highest incidence occurred in those with severe attacks who had urgent ERCP

The overall incidence of pancreas divisum in patients in whom pancreatograms were obtained both during the first hospital admission and subsequently was 10 out of 133 cases

Table 1 *Details of sex, age and admission serum amylase in relation to aetiology, predicted severity and timing of ERCP in all 166 patients*

Gallstones as cause of acute pancreatitis	Predicted severity	ERCP at <72 h			ERCP at 3–30 days			ERCP at 1–6 months		
		M/F	Age*	Amylase*	M/F	Age	Amylase	M/F	Age	Amylase
Yes	Severe	9/17	74 (38–85)	5271 (1300–18000)	3/9	69 (52–85)	4957 (1300–11440)	3/5	67 (39–94)	4670 (1530–13000)
	Mild	13/16	63 (28–86)	5060 (1450–14256)	15/18	66 (28–86)	3100 (1120–17160)	3/5	57 (32–92)	6500 (1460–14000)
No	All cases	3/10	51 (20–83)	6250 (8076–17150)	15/3	52 (20–75)	2388 (900–8480)	13/6	48 (24–79)	3900 (1130–12000)

* Values of age (years) and admission serum amylase (units/l) are given as median (range); ERCP, endoscopic retrograde cholangiopancreatography

Table 2 *Incidence of cholangiography and pancreatography in relation to cause of acute pancreatitis, predicted severity and timing of ERCP in relation to the first day of the attack*

Gallstones as cause of acute pancreatitis	Predicted severity	ERCP at <72 h	ERCP at 3–30 days	ERCP at 1–6 months
		Duct filled/total	Duct filled/total	Duct filled/total
		ERC	ERC	ERC
Yes	Severe	23/26 (88%)	12/12 (100%)	7/8 (88%)
	Mild	26/29 (90%)	33/33 (100%)	7/8 (88%)
No	All cases	11/13 (85%)	15/18 (83%)	15/19 (79%)
		ERP	ERP	ERP
Yes	Severe	13/26 (50%)	9/12 (75%)	8/8 (100%)
	Mild	22/29 (76%)	29/33 (88%)	7/8 (88%)
No	All cases	12/13 (92%)	14/18 (78%)	19/19 (100%)

ERCP, endoscopic retrograde cholangiopancreatography; ERC, cholangiography; ERP, pancreatography

(7·5 per cent). Five of the 22 patients with idiopathic pancreatitis had pancreas divisum as opposed to only 2 of the 88 with gallstone pancreatitis and 3 of the 23 with alcohol-associated pancreatitis ($\chi^2 = 11{\cdot}8$, d.f. = 2, $P < 0{\cdot}01$).

The mean values of the common bile duct and pancreatic duct diameters, age and admission serum bilirubin levels according to aetiological groups, are given in *Table 5*; the statistical differences between these are summarized in *Table 6*. The admission serum amylase was not statistically different between any of these major groups or sub-groups.

Correlation coefficients between these variables are given in *Table 7*. Partial correlation analysis revealed that the significant correlations between common bile duct and pancreatic duct diameters in both the gallstone and no-gallstone groups were still apparent after controlling for age. In the case of the latter group, this correlation was largely due to the positive correlation of the idiopathic group. Similar results were obtained for the correlation between the admission serum bilirubin and common bile duct diameter. A positive correlation between the admission serum bilirubin and the pancreatic duct diameter was also evident in patients with and without gallstones including those in the alcoholic/other groups of patients. No correlation between the admission serum amylase and any of the above factors was found in any of the major groups or sub-groups.

The relationship of common bile duct stones with duct diameters, as well as the association with the serum bilirubin, was also determined in relation to the timing of ERCP and the predicted severity of the attack. *Table 8* shows that there were no significant differences in age between these subgroups The common bile duct diameters were significantly different in all cases. The pancreatic duct diameters were significantly different in those with predicted mild attacks. Although there was no difference between the pancreatic duct diameters in those with predicted severe attacks, it should be noted that pancreatic filling occurred in only 50 per cent of those with choledocholithiasis compared with 95 per cent of those without ($\chi^2 = 7{\cdot}47$, d.f. = 1, $P = 0{\cdot}0064$); by comparison, in the predicted mild groups the incidence of pancreatic filling was identical (82 per cent) in those with and without common bile duct stones. Finally, the admission serum bilirubin was also significantly different in all those who had urgent ERCP and also in mild cases that had early ERCP.

Because an earlier analysis had shown that an admission serum bilirubin >40 μmol/l was a good predictor of choledocholithiasis[26], the value of this was determined in the present series of 120 cases in whom cholangiograms were obtained during the same admission. Of 37 patients with common bile duct stones, 29 had a bilirubin >40 μmol/l compared with 19 of 83 patients without stones. The sensitivity was therefore 78·4 per cent and the specificity was 77 per cent. The predictive value of a positive result was 77·1 per cent and of a negative result was 86·7 per cent.

Details of complications that occurred in all 131 patients who had urgent or early ERCP and endoscopic sphincterotomy as indicated are shown in *Table 9*. Of the 15 pseudocysts which occurred, 11 were already apparent at the time of ERCP, as indicated by endoscopic pancreatography, ultrasonography or CT examinations. Five patients required drainage of symptomatic pseudocysts but in all instances these pseudocysts were already present at the time of ERCP. These pseudocysts were drained at between 3 and 8 weeks after the start of the attack. Four patients with non-infected pseudocysts were treated by internal drainage. One patient with an infected pseudocyst had external drainage. This patient also had multiple liver and peripancreatic abscesses associated with acute cholangitis. In this latter case, ERCP and endoscopic sphincterotomy preceded surgery by 24 h. In the other patients, ERCP preceded surgery by 2–6 weeks. Disseminated intravascular coagulation occurred in a 62-year-old woman with gallstones and predicted severe attack, in whom urgent ERCP was not possible because of ampullary obstruction. Lumbar osteitis occurred as a late presentation in a 73-year-old man with ascending cholangitis and a predicted mild attack who had an urgent endoscopic sphincterotomy. Empyema of the gallbladder also followed an early endoscopic sphincterotomy in a 75-year-old man with ascending cholangitis and a predicted severe attack. With these seven exceptions, all the other complications were apparent by the time ERCP with or without sphincterotomy was undertaken.

Four patients with pancreatic necrosis underwent sequestrectomy with two deaths: one occurred in a 63-year-old man who also had multisystem failure associated with surgery for hyperparathyroidism; the second death occurred in a 71-year-old woman with gallstones who had a pancreatic abscess, subphrenic abscess and respiratory failure. There were two other deaths: one occurred in a 52-year-old woman with gallstones with fulminant pancreatitis, pancreatic necrosis and multisystem failure. The other death occurred in an 84-year-old woman with multisystem failure and pancreatic necrosis; gallstones were not confirmed in this patient despite ascending cholangitis (with positive blood cultures) being apparent. Although all four patients who died had a successful ERCP, in no case were common bile duct stones identified. ERCP did not appear to affect the fulminant clinical course in these patients and was considered to be non-contributory to death.

The incidence of complications relative to predicted severity, timing of ERCP with or without sphincterotomy and the presence of co-existing acute cholangitis for the gallstone group is shown in *Table 10*, and for the no-gallstone group in

Table 4 *Incidence of common bile duct stones in patients with successful cholangiography relative to predicted severity and timing of ERCP*

	Common bile duct stones/total				
Timing of ERCP	Predicted severe	Predicted mild	χ^2	d.f.	P
<72 h	14/23 (61%)	9/26 (35%)	8·43	3	<0·05
3–30 days	6/12 (50%)	8/33 (24%)			
All cases	20/35 (57%)	17/59 (29%)	7·39	1	=0·0066

ERCP, endoscopic retrograde cholangiopancreatography

Table 3 *Incidence of gallbladder filling in cases of successful cholangiography during ERCP, in relation to cause of acute pancreatitis, predicted severity and timing of ERCP in relation to the first day of the attack*

Gallstones as cause of acute pancreatitis	Predicted severity	ERCP at <72 h	ERCP at 3–30 days	ERCP at 1–6 months
		GB filled/total	GB filled/total	GB filled/total
Yes	Severe	14/22 (1), 64%	8/11 (1); 73%	5/6 (1); 83%
	Mild	17/23 (3); 74%	26/29 (4); 90%	6/7, 86%
No	All cases	10/11, 91%	14/15; 93%	14/15; 93%

ERCP, endoscopic retrograde cholangiopancreatography; GB, gallbladder; numbers in parentheses indicate numbers of patients who had previously undergone a cholecystectomy

Table 5 *Mean values of the common bile duct and pancreatic duct diameters, age and admission (<48 h) serum bilirubin according to aetiological groups*

	CBD diameter (mm)			PD diameter (mm)			Age (years)			Bilirubin (μmol/l)		
Group	*n*	Mean	(s.d.)	*n*	Mean	(s.d.)	*n*	Mean	(s.d.)	*n*	Mean	(s.d.)
Gallstones												
No CBD stones	57	7·1	(2·7)	51	3·45	(1·06)	63	62	(15)	63	37	(46)
CBD stones	37	12·5	(4·9)	24	4·02	(1·43)	37	69	(14)	37	83	(53)
All cases	94	9·2	(4·5)	75	3·63	(1·21)	100	65	(15)	100	54	(53)
No gallstones												
Idiopathic	14	5·2	(2·2)	15	3·13	(1·69)	17	55	(17)	17	25	(43)
Alcoholic/others	12	4·8	(1·5)	11	3·22	(1·51)	14	42	(17)	14	26	(32)
All cases	26	5·0	(1·9)	26	3·10	(1·57)	31	49	(17)	31	25	(38)

CBD, common bile duct; PD, pancreatic duct

Table 6 *Statistical comparisons of data given in* Table 5

		Gallstone pancreatitis		
No-gallstone pancreatitis		No CBD stones	CBD stones	All cases
CBD diameter		<0·0001(**)		
Idiopathic	n.s.	0·0161(*)	<0·0001(†)	0·0003(*)
Alcoholic/other		0·0029(*)	<0·0001(*)	<0·0001
All cases		0·0068(**)	<0·0001(†)	<0·0001(**)
PD diameter		n.s.		
Idiopathic	n.s.	n.s.	n.s.	n.s.
Alcoholic/other		n.s.	0·0985	n.s.
All cases		n.s.	0·0332	0·0592
Age		<0·0349		
Idiopathic	0·0567	0·0860	0·0062	0·0232
Alcoholic/other		0·0005	<0·0001	0·0001
All cases		0·0004	<0·0001	<0·0001
Bilirubin		<0·0001		
Idiopathic	n.s.	0·0291	<0·0001(**)	0·0013
Alcoholic/other		n.s.	0·0001(*)	0·0249
All cases		0·0650	<0·0001(†)	<0·0006

CBD, common bile duct; PD, pancreatic duct; significant values using analysis of covariance, with age as a covariate, are also shown as follows: * $P<0{\cdot}05$; ** $P<0{\cdot}01$; † $P<0{\cdot}001$

Table 11. The incidence of co-existing cholangitis in those with confirmed gallstones was significantly greater in those with predicted severe attacks (34 per cent) compared with those with predicted mild attacks (16 per cent) ($\chi^2=4{\cdot}35$, d.f. = 1, $P=0{\cdot}0366$). The incidence of complications in gallstone patients was greater in the predicted severe cases compared with those predicted mild ($\chi^2=5{\cdot}86$, d.f. = 1, $P=0{\cdot}0156$). Patients with choledocholithiasis also had more complications than those without ($\chi^2=6{\cdot}89$, d.f. = 1, $P=0{\cdot}0088$). Patients with predicted severe attacks with choledocholithiasis had the greatest morbidity and those with predicted mild attacks and no common bile duct stones the least morbidity ($\chi^2=9{\cdot}09$, d.f. = 3, $P<0{\cdot}05$).

Discussion

This study is in agreement with other studies which have shown a higher incidence of choledocholithiasis in the first 3 days of the attack (63–78 per cent)[10,15,27] compared with a few days or months later (3–33 per cent)[13–15,27–29]. Patients with predicted severe attacks also had a higher incidence of common bile duct stones; this was only partly accounted for by the fact that patients with predicted severe attacks were older although age was also correlated with the presence of common bile duct stones.

A crucial question relating both to pathogenesis and treatment is whether common bile duct stones cause obstruction of the biliary tree and pancreatic system. There are several lines of evidence from this study to suggest that this is indeed the case.

Patients with common bile duct stones had significantly greater common bile duct diameters. A potential confounding factor is that age was strongly correlated with the bile duct diameter in all patients, including those without gallstones. We have found that this correlation also pertained to a large group of patients with and without gallstones in the absence of a history of acute pancreatitis (unpublished data). Although this conflicts with previously published ERCP studies[24,30–32], our analysis involved larger numbers of patients. Furthermore, it supports the findings of Faris *et al.* who studied the common bile duct with peroperative cholangiography[33]. Even allowing for age, common bile duct diameters were still greater in those with choledocholithiasis in this study. Armstrong *et al.* using peroperative cholangiography did not find such a difference in patients with acute pancreatitis[29]. This difference may reflect the smaller numbers involved, and the fact that neither age nor radiological magnification factor were taken into account[29].

The admission level of serum bilirubin was significantly higher in patients with choledocholithiasis, again taking age into account. Moreover, a significant correlation was shown between the bilirubin level and common bile duct diameter. A previous analysis had shown that the bilirubin level was the single most significant indicator of common bile duct stones in acute pancreatitis[26]. In contrast, the serum transaminase was not significant in this respect[26]. The initial large increase in transaminase level observed in gallstone pancreatitis probably reflects a very transient rise in biliary pressure owing to a migrating stone[26,34], whereas the admission bilirubin level reflects relatively acute obstruction of the biliary tree. Further evidence to support this comes from analysis of patients with common bile duct stones not associated with acute pancreatitis, who, despite having high bilirubin levels, demonstrated no relationship between the duct diameter and bilirubin level (unpublished data).

Pancreatic duct diameter during acute pancreatitis depends upon (1) the pre-existing diameter, (2) the degree of obstruction causing dilatation, and (3) the degree of surrounding pancreatic inflammation tending to compress the duct In this study we found strong correlations between age and the pancreatic duct diameter and also between the common bile duct and pancreatic duct diameters. We have also observed the same relationship in patients with and without gallstones unrelated to acute pancreatitis (unpublished data). The correlation between duct diameters was sustained even allowing for age. As might be anticipated from the correlation between the diameter of the common bile duct and the admission serum bilirubin level, a strong correlation was also evident between pancreatic duct diameter and bilirubin level. The diameter of the pancreatic duct was greater in patients with choledocholithiasis and a predicted mild attack than in those with predicted severe attacks. However, whereas the incidence of bile duct filling was similar in all groups who underwent urgent ERCP, the incidence of pancreatic duct filling was significantly lower in those with predicted severe attacks and gallstones (*Table 2*). More-

Table 7 *Correlation coefficients between common bile duct and pancreatic duct diameters, admission (<48 h) serum bilirubin and age in each of the aetiological groups*

	CBD *versus* PD diameter			Bilirubin *versus* CBD diameter			Bilirubin *versus* PD diameter			Age *versus* CBD diameter			Age *versus* PD diameter			Age *versus* bilirubin		
Group	*n*	*r*	*P*	*n*	*r*	*P*	*n*	*r*	*P*	*n*	*r*	*P*	*n*	*r*	*P*	*n*	*r*	*P*
Gallstones																		
No CBD stones	47	−0·036	n.s.	57	0·155	n.s.	51	0·147	n.s.	57	−0·190	n.s.	51	0.021	n.s.	63	0·255	n.s.
CBD stones	24	0·488	<0·02	37	0·240	n.s.	24	0·318	n.s.	37	0·516	<0·001	24	0·499	<0·01	37	0·165	n.s.
All cases	71	0·317	<0·01*	94	0·396	<0·001†	75	0·291	<0·01*	94	0·322	<0·01	75	0·234	<0·05	100	0·266	<0·01
No-gallstones																		
Idiopathic	14	0·780	<0·001*	14	0·905	<0·001†	15	0·593	<0·05	14	0·667	<0·01	15	0·689	<0·01	17	0·476	<0·05
Alcoholic/other	11	−0·016	n.s.	12	−0·113	n.s.	11	0·760	<0·001†	12	0·552	<0·05	11	0·061	n.s.	14	−0·180	n.s.
All cases	25	0·620	<0·001**	26	0·737	<0·001†	26	0·680	<0·001†	26	0·620	<0·001	26	0·373	<0·05	31	0·262	n.s.

CBD, common bile duct; PD, pancreatic duct, * controlling for age $P < 0·05$, ** controlling for age $P < 0·01$, † controlling for age $P < 0·001$

Table 8 *Comparisons of common bile duct and pancreatic duct diameters, age and admission (<48 h) serum bilirubin levels in relation to the presence or absence of common bile duct stones at the time of ERCP, the predicted severity and the timing of ERCP*

CBD stones present	Time of ERCP	Predicted severity	CBD diameter (mm)			PD diameter (mm)			Age (years)			Bilirubin (μmol/l)			*P* CBD stones *versus* no CBD stones			
			n	Mean	(s.d.)	*n*	Mean	(s.d.)	*n*	Mean	(s.d.)	*n*	Mean	(s.d.)	CBD	PD	Age	Bilirubin
Yes	<72 h	Severe	14	13·2	(6·0)	6	3·00	(0·89)	14	70	(50)	14	88	(50)	0·0438	n.s.	n.s.	0·0146
		Mild	9	11·4	(4·6)	6	3·83	(1·61)	9	63	(18)	9	85	(59)	0·0043	n.s.	n.s.	0·0209
	3–30 days	Severe	6	14·0	(3·0)	4	4·68	(2·15)	6	72	(14)	6	81	(64)	0·0163	n.s.	n.s.	n.s.
		Mild	8	11·1	(4·4)	8	4·60	(0·85)	8	71	(7)	8	73	(49)	0·0063	0·0068	n.s.	0·0039
	Total 1–30 days	Severe	20	13·5	(5·2)	10	3·67	(1·65)	20	70	(13)	20	86	(53)	0·0019	n.s.	n.s.	0·090
		Mild	17	11·3	(4·3)	14	4·27	(1·24)	17	67	(14)	17	79	(53)	<0·001	0·0438	n.s.	<0·0001
No	<72 h	Severe	9	8·2	(3·6)	9	3·22	(0·83)	12	70	(11)	12	43	(48)				
		Mild	17	7·2	(2·2)	16	3·56	(1·15)	20	61	(16)	20	28	(40)				
	3–30 days	Severe	6	7·7	(2·6)	5	4·2	(1·10)	6	67	(5)	6	108	(73)				
		Mild	25	6·6	(2·6)	21	3·29	(1·06)	25	59	(18)	25	24	(23)				
	Total 1–30 days	Severe	15	8·0	(3·2)	14	3·57	(1·02)	18	69	(9)	18	65	(64)				
		Mild	42	6·8	(2·5)	37	3·41	(1·09)	45	60	(17)	45	26	(31)				

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; PD, pancreatic duct

Table 9 *Details of complications in all 131 patients who had urgent or early ERCP with or without endoscopic sphincterotomy*

Complications	Total	Complications possibly due to ERCP ± ES
Pseudocysts	15	4
Pancreatic necrosis	6 (4†)	0
Pancreatic abscess	4 (1†)	0
Pancreatic fistula	1	0
Liver abscess	1	0
Peripancreatic abscess	3	0
Pseudo-obstruction	1	0
Disseminated intravascular coagulation	1	1
Respiratory failure	5 (1†)	0
Multisystem failure	3 (3†)	0
Lumbar osteitis	1	1
Empyema of gallbladder	1	1
Deaths	4 (3·1%)	0
Number of patients with complications	23 (17·6%)	7 (5·3%)

ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy.
†Number of complications associated with death

over, the pancreatic duct filled in only 50 per cent of severe attack patients with common bile duct stones but in 95 per cent of those without choledocholithiasis, yet the technique of cannulation at ERCP was similar in all patients. This indicates that the reduced incidence of pancreatic duct filling in severe cases was related to the presence of common bile duct stones. Possible mechanisms of action include direct pancreatic duct obstruction by the stones, increased oedema or 'pancreatitis' in the head of the gland, and increased spasm of the pancreatic duct sphincter.

A greater pancreatic duct diameter in patients with gallstone pancreatitis compared with those with gallstones and no pancreatitis was observed by Armstrong *et al.*[29] using peroperative cholangiography. However, this observation must be interpreted in the light of reservations identical to those expressed for measurement of common bile duct diameters in the same study; moreover, only 15 per cent of the non-pancreatitis group had pancreatic duct reflux, compared with 62 per cent in the pancreatitis group, possibly compounding apparent rather than real differences. Nevertheless, our findings provide confirmation of this important original observation.

The present study has established that there is a strong (but not invariable) association between persisting common bile duct stones, predicted severe attacks and an increased complication rate. Indeed the complication rate in patients with predicted mild attacks and choledocholithiasis was higher than in those with predicted severe attacks and no common bile duct stones and almost as high as in those with common bile duct stones in the severe attack group. It should be noted, however, that the incidence of common bile duct stones is much lower in those with predicted mild attacks.

Of all patients in the gallstone pancreatitis group, the overall complication rate was 19 per cent with a mortality of only 2 per cent. At most, only seven of the nineteen complications could in any way be attributed to ERCP with or without endoscopic sphincterotomy; indeed, in our opinion only two of the complications could be so attributed (one case of empyema of the gallbladder and one case of lumbar osteitis). It is noteworthy that none of the 37 patients in this study treated by endoscopic sphincterotomy died. In recent years the mortality from gallstone pancreatitis in Leicester has fallen from

Table 10 *Incidence of complications in patients with gallstones relative to predicted severity, timing of ERCP with or without endoscopic sphincterotomy and the presence of co-existing ascending cholangitis*

Predicted severity	Time of ERCP	Ascending cholangitis	ERCP only (n)	Complications		ES (n)	Complications		ERCP ±ES (n)	Complications	
				Total	?ERCP*		Total	?ES*		Total	?ERCP ±ES*
Severe	<72 h	7	12	3†	2	14	3	0	26	6†	2
	3–30 days	6	6	1†	0	6	4	1	12	5†	1
	Subtotal	13	18	4‡ (22%)	2	20	7 (35%)	1	38	11‡ (29%)	3
Mild	<72 h	2	20	0	0	9	4	2	29	4	2
	3–30 days	8	25	3	2	8	1	0	33	4	2
	Subtotal	10	45	3 (7%)	2	17	5 (29%)	2	62	8 (13%)	4
All cases		23	63	7‡ (11%)	4	37	12 (32%)	3	100	19‡ (19%)	7

ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy.
* Complications possibly related to ERCP ± ES out of the total given; † includes one death; ‡ includes both deaths

Table 11 *Incidence of complications in all patients without gallstones in relation to predicted severity*

Predicted severity	Ascending cholangitis	ERCP (n)	Complications	
			Total	?ERCP*
Severe**	1	9	4† (44%)	0
Mild***	0	22	0	0
All cases	1	31	4† (13%)	0

ERCP, endoscopic retrograde cholangiopancreatography.
* Complications possibly related to ERCP; ** 3 ERCPs performed <72 h; *** 10 ERCPs performed <72 h; † includes two deaths (6·4% of total).

around 11 per cent to 7 per cent in those not managed with ERCP with or without endoscopic sphincterotomy. Mortality rates elsewhere, using conventional management, have also tended to mirror this decline, but range from around 5 per cent to 20 per cent[14,19,29,35–38]. In contrast, in a collection of seven series totalling 152 cases of gallstone pancreatitis treated by endoscopic sphincterotomy, the mortality was only 2·6 per cent[39]. Inclusion of the present 37 cases reduces this overall mortality to 2 per cent.

Despite the introduction of percutaneous methods of treating pseudocysts[40], our preference is for internal surgical drainage. There was no evidence that ERCP with or without endoscopic sphincterotomy introduced infection in pseudocysts in our limited experience, although this is a significant potential hazard[41]. Unless patients are being considered for percutaneous aspiration or drainage[40], we do not see any role for ERCP in the diagnosis or treatment of pancreatic pseudocysts.

Although our study was primarily directed at patients with gallstone-associated pancreatitis, analysis of patients with non-gallstone pancreatitis reveals some tantalizing information. Despite the small numbers studied, the no-gallstone patients were found to have highly significant correlations between the pancreatic and common bile duct diameters, and both of these were correlated with the admission serum bilirubin. These differences were largely attributable to the idiopathic group of patients. Although this may suggest that these patients have in fact all had gallstones and passed them, we suspect that this is not so for the great majority. Virtually all of these patients have also undergone 'late' ultrasound examinations and bile crystal analysis[42], and while they do not appear to have gallstones we believe that they behave in a similar manner to patients who do have stones. The cause of the obstruction in this group may be a functional motility disorder of the sphincter of Oddi as shown by Toouli *et al.*[43]. The increased incidence of pancreas divisum in the patients in the present study may possibly relate to an increased predisposition to sphincter dysfunction. Arguing along similar lines, it is conceivable that one mechanism implicated in alcohol-induced acute pancreatitis is increased sphincter sensitivity to alcohol.

The benefits of urgent ERCP with or without endoscopic sphincterotomy in patients with suspected gallstones compared with conventional management have recently been established in a prospective randomized trial, which included some of the present patients[21]. This approach showed benefit in terms of outcome only in those with predicted severe attacks (reduction in morbidity from 61 per cent to 18 per cent and in mortality from 24 per cent to 4 per cent). The results of the study described here allow us to reach the following general conclusions:

1. Whereas migrating stones are important in initiating the attack of acute pancreatitis, persisting common bile duct stones are important in determining the complication rate, probably by causing acute obstruction of both the common bile duct and pancreatic duct.
2. The results of our trial support the view that urgent ERCP should be undertaken in patients with predicted severe attacks and suspected gallstones. If stones are found, endoscopic sphincterotomy should be performed and the stones extracted.
3. However, all patients (irrespective of the predicted severity of their attack) who fail to progress, or develop complications necessitating surgery, should also undergo ERCP. Stones may be found and endoscopic sphincterotomy may avoid the need for dangerous surgery to the biliary tract or duodenum. This combined approach has undoubtedly contributed to a reduced mortality rate in our patients.
4. The present study has confirmed that an admission serum bilirubin value of >40 μmol/l is a good predictor of persisting common bile duct stones and may be valuable in deciding whether to undertake an ERCP.
5. Finally, we wish to emphasize that ERCP with or without endoscopic sphincterotomy forms only one aspect of management. The best results are achieved by using these techniques in conjunction with proper monitoring, adequate supportive care and judicious surgery. It is essential that ERCP and sphincterotomy should be undertaken only by skilled endoscopists.

Acknowledgements

We are indebted to all the consultant surgeons and physicians in Leicester who have allowed us to study their patients. This study would not have been possible without the invaluable assistance of the Departments of Radiology, Biochemistry and Haematology, the junior surgical and medical staff, the endoscopy units and our nursing sisters and their staff (involving all the Leicester hospitals). We are extremely grateful to Mrs Dilys Thomas for her secretarial assistance.

References

1. Moynihan B. Acute pancreatitis. *Ann Surg* 1925; **81**: 132–42.
2. Mayo WJ. The surgical treatment of pancreatitis. *Surg Gynecol Obstet* 1908, **6**: 607–13.
3. Deaver JB, Sweet JE. Prepancreatic and peripancreatic disease. *JAMA* 1921; **77**. 194–7.
4. Opie EL. The etiology of acute hemorrhagic pancreatitis. *Johns Hopkins Hosp Bull* 1901, **121**: 182–8.
5. Mikkelsen O. Pancreatitis acuta; schwere Falle, besonders hinschtligh ihrer konservativen Behandlung *Acta Chir Scand* 1934, **75**: 373–415
6. Kelly TR Gallstone pancreatitis. pathophysiology. *Surgery* 1976, **80**: 488–92.
7. Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. *N Engl J Med* 1974; **290**. 484–7.
8. Mayer AD, McMahon MJ Gallstones and acute pancreatitis—is the association underestimated? (Abstract) *Br J Surg* 1986; **71** 905.
9. Acosta JM, Rossi R, Galli OMR, Pellegrini CA, Skinner DB Early surgery for acute gallstone pancreatitis: evaluation of a systematic approach. *Surgery* 1978; **83**. 367–70.
10. Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis: biliary tract pathology in relation to time of operation. *Ann Surg* 1981; **194**: 305–10
11. Mercer LC, Saltzstein EC, Peacock JB, Dougherty SH. Early surgery for biliary pancreatitis. *Am J Surg* 1984; **148**: 749–51.
12. Skinner DB Should early surgical intervention be routinely recommended in the management of gallstone pancreatitis? Affirmative. In: Gitnick G, ed. *Controversies in Gastroenterology*. London· Churchill Livingstone, 1984· 197–203.
13. Paloyan D, Simonowitz D, Skinner DB. The timing of biliary tract operations in patients with pancreatitis associated with gallstones. *Surg Gynecol Obstet* 1975; **141**: 737–9.
14. Ranson JHC. The timing of biliary surgery in acute pancreatitis. *Ann Surg* 1979; **189**: 654–62
15. Kelly TR. Gallstone pancreatitis. The timing of surgery. *Surgery* 1980; **88**: 345–9.
16. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone-associated acute pancreatitis. *Br J Surg* 1981, **68**: 758–61.
17. Tondelli P, Stutz LK, Harder F, Schuppisser JP, Allgower M. Acute gallstone pancreatitis: best timing for biliary surgery. *Br J Surg* 1982; **69**. 709–10
18. Cuschieri A, Cumming JGR, Wood RAB, Baker PR. Evidence for sphincter dysfunction in patients with gallstone associated pancreatitis—effect of ceruletide in patients undergoing cholecystectomy for gallbladder disease and gallstone associated pancreatitis. *Br J Surg* 1983; **71**: 885–8.
19. Imrie CW, Benjamin IS, Ferguson JC *et al* A single centre double-blind trial of Trasylol therapy in primary acute pancreatitis. *Br J Surg* 1978; **65**· 337–41.
20. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984; **25**: 1340–6.
21. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP Results of a prospective randomized trial of ERCP and endoscopic sphincterotomy in acute pancreatitis due to gallstones (Abstract). *Gut* 1988; **29**: A266.
22. Dunne MJ, Shenkin A, Imrie CW Misleading hyponatraemia in acute pancreatitis with hyperlipaemia (Letter) *Lancet* 1979; **i**. 211.
23. Carr-Locke DL, Cotton PB. Biliary tract and pancreas. *Br Med Bull* 1986; **42**: 257–64.
24. O'Dwyer JA, Pemberton J, Thompson RPH. Measurement of the endoscopic retrograde cholangiogram *Dig Dis Sci* 1981; **28**: 561–4
25. Morrison DF. *Multivariate Statistical Methods* London: McGraw-Hill International Book Company, 1981: 93–4.
26. Neoptolemos JP, London N, Bailey I *et al.* The role of clinical and biochemical criteria and endoscopic retrograde cholangiopancreatography in the urgent diagnosis of common bile duct stones in acute pancreatitis. *Surgery* 1987; **100**: 732–42
27. Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute biliary pancreatitis. *Surgery* 1980; **88**· 118–25.
28. Dixon JA, Hillam JD. Surgical treatment of biliary tract disease associated with acute pancreatitis. *Am J Surg* 1970, **120**: 371–5.
29. Armstrong CP, Taylor TV, Jeacock J, Lucas S The biliary tract in patients with acute gallstone pancreatitis. *Br J Surg* 1985, **72**: 551–5.
30. Kasugai T, Kuno N, Kobayashi S, Hattori K. Endoscopic pancreatocholangiography. I. The normal endoscopic pancreatocholangiogram. *Gastroenterology* 1972; **63**. 217–26.
31. Belsito AA, Marta JB, Cramer GG, Dickinson PB. Measurement of biliary tract size and drainage time. *Radiology* 1977; **122**. 65–9
32. Hamilton I, Ruddell WSJ, Mitchell CJ, Lintott DJ, Axon ATR. Endoscopic retrograde cholangiograms of the normal and post-cholecystectomy biliary tree *Br J Surg* 1982; **69**· 343–5.
33. Faris I, Thompson JPS, Grundy DJ, Le Quesne LP. Operative cholangiography· a reappraisal based on a review of 400 cholangiograms. *Br J Surg* 1975; **62**: 966–72.
34. Mayer AD, McMahon MJ. Biochemical identification of patients with gallstones associated with acute pancreatitis on the day of admission to hospital *Ann Surg* 1985; **201**. 68–75.
35. Corfield AP, Cooper MJ, Williamson RCN *et al.* Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices *Lancet* 1985; **ii**: 403–7.
36. DeBolla AR, Obeid ML Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6.
37. Mayer AD, McMahon MJ, Benson EA, Axon ATR Operations upon the biliary tract in patients with acute pancreatitis: aims, indications and timing. *Ann R Coll Surg Engl* 1984; **66**· 179–83.
38. MRC Multicentre Trial. Death from acute pancreatitis. *Lancet* 1977; **ii**: 632–5.
39. Neoptolemos JP, Carr-Locke DL. ERCP in acute cholangitis and pancreatitis. In: Jacobson I, ed. *ERCP: Techniques and Therapeutic Application*. New York: Elsevier Publishing Co Inc, 1988. in press.
40. Van Sonnenberg E, Wittich GR, Casola G *et al.* Complicated pancreatic inflammatory disease· diagnostic and therapeutic role of interventional radiology. *Radiology* 1985, **155**: 335–40.
41. O'Connor M, Kolars J, Ansel H, Silvis S, Venes J. Pre-operative endoscopic retrograde cholangiopancreatography in the surgical management of pancreatic pseudocysts. *Am J Surg* 1986; **151**: 18–23.
42. Neoptolemos JP, Davidson BR, Winder AF, Vallance D. The role of duodenal bile crystal analysis in the investigation of 'idiopathic' pancreatitis *Br J Surg* 1988, **75**: in press.
43. Toouli J, Roberts-Thomson IC, Dent J, Lee J. Sphincter of Oddi motility disorders in patients with idiopathic recurrent pancreatitis. *Br J Surg* 1985; **72**: 859–63

Br. J. Surg. 1988, Vol. 75, October,
961–965

A prospective comparison of the effects of placebo, ranitidine and highly selective vagotomy on 24 h ambulatory intragastric pH in patients with duodenal ulcer

Twenty-four hour ambulatory intragastric pH (24 h IGpH) recording, a highly reproducible technique, was used to compare the effects of ranitidine and highly selective vagotomy (HSV) in 20 patients who had been referred for surgical treatment of duodenal ulcer. The 24 h IGpH was recorded when they were taking either placebo or ranitidine 300 mg at 10 pm, and again 4 to 13 weeks after elective HSV. Median 24 h IGpH and 24 h hydrogen ion activity (24 h $[H^+]$*) were calculated for each patient. Median (quartile) 24 h IGpH was 1·4 (1·3–1·6) with placebo, 2·2 (1·8–2·7) after ranitidine and 2·6 (1·8–3·7) after HSV. IGpH was significantly higher after both ranitidine (*$P<0{\cdot}0001$*) and HSV (*$P<0{\cdot}0001$*) than after placebo, but IGpH after ranitidine did not differ from IGpH after HSV (*$0{\cdot}5>P>0{\cdot}4$*). HSV reduced 24 h* $[H^+]$ *by a median 68 per cent (quartiles, 47–82 per cent) whereas ranitidine reduced it by only 50 per cent (34–69 per cent,* $0{\cdot}1>P>0{\cdot}05$*). The 24 h pH recording was then analysed as two distinct periods; 'daytime' (8 am to midnight) and 'night-time' (midnight to 8 am). HSV reduced daytime* $[H^+]$ *by a median 77 per cent (59–93 per cent) whereas ranitidine reduced it by only 30 per cent (13–45 per cent,* $P<0{\cdot}0001$*). HSV reduced night-time* $[H^+]$ *by a median 57 per cent (40–83 per cent) but ranitidine reduced it by a median 92 per cent (78–98 per cent,* $P<0{\cdot}01$*). Thus, HSV inhibits gastric acidity more during the day than at night, whereas raniditine given at 10 pm effectively suppresses night-time acidity but is much less effective in suppressing daytime acidity. However both HSV and ranitidine will heal more than 90 per cent of duodenal ulcers. Hence, contrary to Dragstedt's teaching, suppression of nocturnal acidity is not of crucial importance for the healing of duodenal ulcers.*

**M. J. Rogers,
J. H. M. Holmfield,
J. N. Primrose,
T. Gledhill* and
D. Johnston**

*University Department of Surgery,
The General Infirmary,
Leeds LS1 3EX, UK
Correspondence to:*
Dr M. J. Rogers

Keywords: Duodenal ulcer, nocturnal acid, highly selective vagotomy, ranitidine, ambulatory pH monitoring

Reduction of gastric acid output is the mainstay of medical and surgical treatment of duodenal ulcer. Dragstedt believed that suppression of nocturnal acid output was particularly important. In 1943, he and Owens reported[1] that transthoracic truncal vagotomy dramatically reduced the copious overnight secretion of acid that they had observed before operation in three patients with duodenal ulcer. This seminal work not only rekindled worldwide interest in the use of vagotomy for duodenal ulcer, but created an enduring impression that inhibition of overnight secretion was more important for the healing of ulcers than inhibition of secretion during the day. More recent work[2] which showed that a single 300 mg dose of ranitidine given in the evening was as effective in ulcer healing as two 150 mg doses given morning and evening lent further weight to this idea.

In the present study, intragastric pH was monitored over a 24 h period in control subjects and in patients with duodenal ulcer to study the effect of ranitidine and highly selective vagotomy (HSV). The findings cast doubt on the idea that overnight secretion is of paramount importance in the pathogenesis and therapy of duodenal ulceration.

Patients and methods

Two groups of subjects were studied. Firstly, 28 healthy male volunteers were studied to assess the reproducibility of serial recordings of 24 h intragastric pH. Secondly, 20 consecutive patients referred for elective operative treatment of duodenal ulcer were studied to assess the effects of ranitidine and HSV. All subjects gave informed consent before the first recording was commenced.

Measurement of 24 h ambulatory intragastric pH

Intragastric pH (IGpH) was monitored using the Medilog 1000 system (John Caunt Scientific Ltd, Oxford, UK), which employs an intragastric radiotelemetry capsule[3] (Remote Control Systems Ltd., London, UK), which incorporates both a glass pH electrode and a cotton thread reference electrode.

The telemetry capsule transmits a continuous, frequency-modulated radio signal to an aerial worn wrapped around the trunk at the level of the xiphoid. A fabric belt holds the aerial in position and two shoulder straps prevent the aerial sliding down the trunk. We showed previously that use of this belt virtually abolishes signal loss during recording of ambulatory intragastric pH with this system[4]. Information is relayed to a data recorder worn on a belt around the waist and the radio signal is sampled every 6 s, thus 14400 measurements of gastric pH are obtained from each patient during a 24 h period.

Before the start of each IGpH recording, the system was calibrated with the telemetry capsule in buffers of pH 1·2 and 7·0 at 37°C

---

* *Mr T. Gledhill was tragically killed in a sailing accident on 9 April 1988 during the course of this paper's preparation*

0007-1323/88/100961-05$3 00

Calibration was repeated after every recording to check that the performance of the telemetry capsule had not altered. The entire 24 h recording was then transferred via a desktop computer to magnetic floppy disc for storage and analysis.

Day-to-day variation in 24 h intragastric pH

Twenty-eight healthy male volunteers of mean age 23 years (range 21–32) with no previous history of peptic ulcer disease had 24 h IGpH recorded on two occasions separated by an interval of 1–5 weeks.

Each subject arrived 45 min before commencement of the pH recording, having fasted for the previous 3 h. The telemetry capsule was tied to a tether and swallowed. The free end of the tether was attached to the skin of the cheek with adhesive tape to prevent onward passage of the telemetry capsule from the stomach. The length of the tether was calculated for each subject from his height, (50 cm for a height of 150 cm, increased 1 cm for every 7·5 cm that the subject's height exceeded 150 cm) and was fixed for each subject for the duration of the study.

When the capsule was in the stomach, the equipment was assembled and pH recording commenced. The subject then went home and returned at the same time the next day.

During the 24 h recording each subject kept a diary of food and fluid intake and the amount of tobacco smoked. The time of going to bed and rising was also recorded. Diet, smoking and sleeping patterns were duplicated, as far as possible, on the second occasion of IGpH recording.

Effects of ranitidine 300 mg nocte *and of highly selective vagotomy on intragastric pH in patients with duodenal ulcer*

Twenty patients, of median age 33 years (range 22–59), who had been referred for elective operation for duodenal ulcer were studied. In each the diagnosis of duodenal ulcer had been verified endoscopically within the previous 6 months. In 13 patients, the indication for operation was frequent attacks of pain or dyspepsia associated with relapse of the ulcer which was confirmed endoscopically; these patients had suffered with duodenal ulceration for a median 11 years (range 1–27). In the remaining seven patients, the indication for surgery was failure of their duodenal ulceration to heal despite 3 months continuous therapy with full dose anti-ulcer medication; these patients had suffered with duodenal ulcer for a median 7 years (range 2–30). In each patient 24 h IGpH was recorded on three occasions.

Before operation, 24 h IGpH was recorded twice in each patient, once when taking placebo and once when on ranitidine 300 mg. Anti-ulcer medication was stopped for 48 h before each of these recordings and the medication was ingested at 10 pm on two consecutive nights: the night before, and the night of IGpH recording.

All patients recorded details of their food and fluid intake and amount of tobacco smoked during each recording, and they were asked to go to bed at 11 pm and to rise at 7–7.30 am. Their actual bedtime and time of rising were recorded, as was the exact time at which the medication was taken. By these means, diet, smoking and sleeping pattern were kept constant for each IGpH recording. Each patient provided a 10 ml urine sample during every IGpH recording; this was stored at −20°C for assay of urinary ranitidine.

Each patient was allowed a 7–14 day interval between the two pre-operative IGpH recordings and the sequence of the placebo and ranitidine IGpH recordings was allocated in a randomized, single-blind manner. For all recordings of IGpH, patients who were working night shifts were studied 7 full days after their last night shift.

A standard insulin test was performed 7–10 days postoperatively following a technique we have previously described[5].

Each patient had 24 h IGpH recorded on a third occasion, 4–13 weeks after HSV, when the diet, smoking and sleeping pattern were identical to those of the pre-operative recordings. No medication, however, was taken on this occasion.

Analysis of data

Each 24 h IGpH recording was analysed to give median and quartile 24 h pH values. In the patients with duodenal ulcer, the 24 h record was also split into 'daytime' (8 am–midnight) and 'night-time' (midnight–8 am): median and quartile, daytime and night-time pH values were also calculated. The 24 h hydrogen ion activity (24 h $[H^+]$) was expressed as the area under the curve of hydrogen ion activity *versus* time. This was computed as the sum of the hydrogen ion activities equivalent to each of the 14 400 pH values provided by a 24 h recording. Daytime $[H^+]$ and night-time $[H^+]$ were similarly computed.

The effects of ranitidine and vagotomy on IGpH were calculated for each patient as the change in 24 h, daytime, and night-time $[H^+]$ compared with the corresponding $[H^+]$ when no active medication (placebo) was taken.

The effects of ranitidine and vagotomy on IGpH were compared by means of non-parametric statistics (Kruskal–Wallis one-way analysis of variance[6]), differences being considered statistically significant when $P < 0{\cdot}05$. As the use of tests which place weight on the magnitude of the difference between variables is not appropriate to comparisons of logarithmic variables, direct comparison of median IGpH values is not appropriate. To avoid this, all median IGpH values were converted to their equivalent hydrogen ion activity before comparisons between groups were made. However, because the use of hydrogen ion activities in graphs and text is cumbersome, the equivalent pH values have been quoted in preference.

The results of the insulin test were expressed as Hollander's criteria[7] and as peak acid response to insulin minus basal acid output.

Graphical presentation of data

Data are represented graphically as scatter plots on which group median values are indicated where appropriate.

Results

The tests were well tolerated by all subjects and no side-effects of the medication or of the IGpH recording procedure were noted. Patients' compliance with instructions was good and all patients took the tablets within 15 min of the time requested. Each patient with duodenal ulcer provided the required urine specimen, and a gas–liquid chromatographic assay showed that ranitidine was present in the urine of each patient who was taking ranitidine and in none of the samples from patients taking placebo.

The median data loss per 24 h IGpH recording over the entire study was 0·5 per cent (quartiles 0·07–2·1 per cent).

Day-to-day variation in 24 h intragastric pH in normal subjects

The median (quartile) 24 h IGpH of 28 normal subjects was 1·5 (1·5–1·7) on the first recording and 1·6 (1·4–1·8) on the second. Median 24 h IGpH on the two occasions did not differ significantly ($0{\cdot}975 > P > 0{\cdot}95$). Likewise, 24 h $[H^+]$ did not differ between the two recordings ($0{\cdot}8 > P > 0{\cdot}7$).

Effects of ranitidine 300 mg nocte *and highly selective vagotomy on intragastric pH in patients with duodenal ulcer*

Insulin tests. The insulin test was not performed in two patients because one suffered from insulin dependent diabetes and the other experienced an episode of fast atrial fibrillation which required cardioversion on the third postoperative day. For the remaining 18 patients the test was positive by Hollander's criteria in only 3, and the median peak acid response to insulin minus basal acid output was only 0·02 mmol/h.

24 h acidity. The median (quartile) 24 h IGpH in 20 patients with duodenal ulcer (*Figure 1*) was 1·4 (1·3–1·6) on placebo, 2·2 (1·8–2·7) on ranitidine 300 mg *nocte* and 2·6 (1·8–3·7) after HSV. Median 24 h IGpH was significantly higher on ranitidine and after HSV than on placebo ($P < 0{\cdot}0001$, $P < 0{\cdot}0001$ respectively). Median 24 h IGpH on ranitidine did not differ significantly from IGpH after HSV ($0{\cdot}5 > P > 0{\cdot}4$), although median hydrogen ion activity after HSV was one-quarter of that after ranitidine.

Median (quartile) suppression of 24 h $[H^+]$ (*Figure 2*) was 50 per cent (34–69) after ranitidine and 68 per cent (47–82) after HSV, but the difference was not quite significant ($0{\cdot}1 > P > 0{\cdot}05$).

Night-time acidity (midnight to 8 am). Median night-time IGpH (*Figure 3*) was 1·2 (1·0–1·4) on placebo, 5·8 (2·8–6·9) on ranitidine and 1·7 (1·4–2·8) after HSV. Both ranitidine and HSV raised night-time IGpH significantly compared with placebo ($P < 0{\cdot}0001$ and $P < 0{\cdot}001$ respectively). Median night-time IGpH was significantly higher after ranitidine than after HSV ($P < 0{\cdot}001$).

Median night-time suppression of $[H^+]$ (*Figure 4*) was

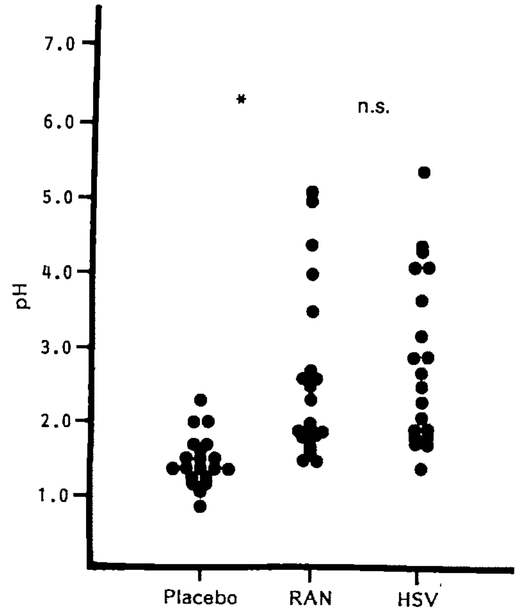


Figure 1 *Median 24 h intragastric pH with placebo, ranitidine 300 mg* nocte (*RAN*) *and after highly selective vagotomy* (*HSV*) *in 20 patients with duodenal ulcer.* $^*P<0{\cdot}0001$, *placebo* versus *RAN and placebo* versus *HSV; n.s., not significant, RAN* versus *HSV*

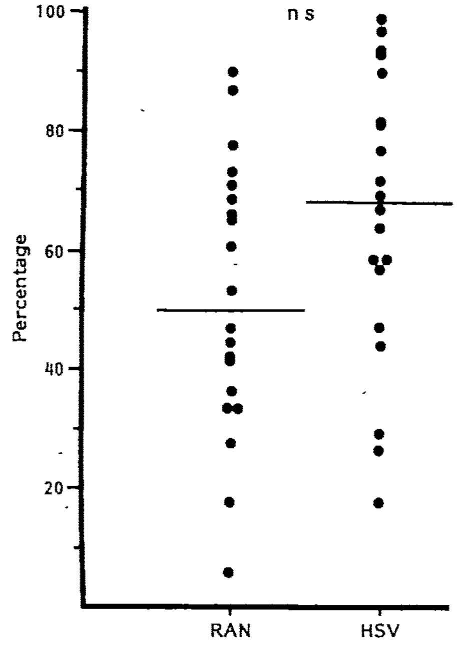


Figure 2 *Twenty-four hour acid suppression after ranitidine 300 mg* nocte (*RAN*) *and after highly selective vagotomy* (*HSV*) *in 20 patients with duodenal ulcer. Lines indicate median values. n.s., Not significant, RAN* versus *HSV*

92 per cent (78–98) after ranitidine and 57 per cent (40–83) after HSV ($P<0{\cdot}01$).

Daytime acidity (*8 am to midnight*). The median daytime IGpH (*Figure 5*) was 1·6 (1·4–1·7) on placebo, 1·8 (1·6–2·1) on ranitidine and 2·7 (2·0–3·8) after HSV. Median daytime IGpH was significantly higher after ranitidine ($P<0{\cdot}02$) and HSV ($P<0{\cdot}0001$) than after placebo. Also, median daytime IGpH after HSV was significantly higher than after ranitidine ($P<0{\cdot}001$).

Median daytime suppression of [H$^+$] (*Figure 6*) was 30 per cent (13–45) after ranitidine and 77 per cent (59–93) after HSV ($P<0{\cdot}0001$).

Discussion

Using a highly reproducible technique, we have shown that ranitidine, given as a 300 mg *nocte* dose, is a more potent suppressor of night-time acidity than is HSV, whereas HSV is a more potent suppressor of daytime acidity than is ranitidine. Over a 24 h period there was no significant difference between suppression of acid after HSV and suppression after ranitidine, 300 mg *nocte*: nevertheless suppression by HSV was much greater than suppression by ranitidine and was almost significant ($0{\cdot}05<P<0{\cdot}1$).

Of the 20 patients studied, 18 had a standard insulin test performed between 7 and 10 days after HSV. The test was positive by Hollander's criteria in only three cases and the median peak acid response to insulin minus basal acid output

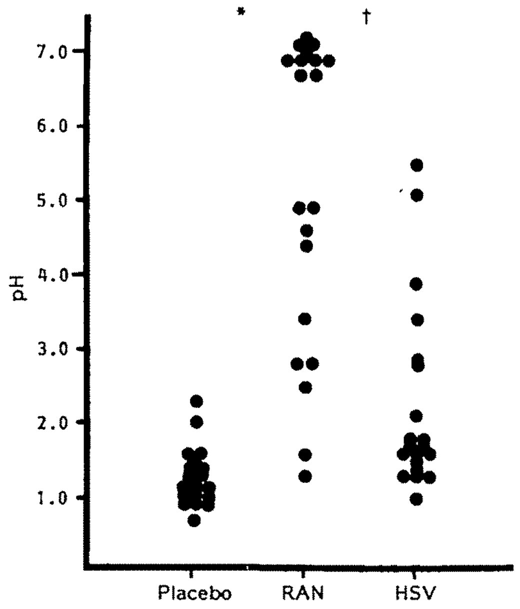


Figure 3 *Median night-time* (*midnight–8 am*) *intragastric pH with placebo, ranitidine 300 mg* nocte (*RAN*) *and after highly selective vagotomy* (*HSV*) *in 20 patients with duodenal ulcer.* $^*P<0{\cdot}0001$, *placebo* versus *RAN;* $^\dagger P<0{\cdot}001$, *placebo* versus *HSV and RAN* versus *HSV*

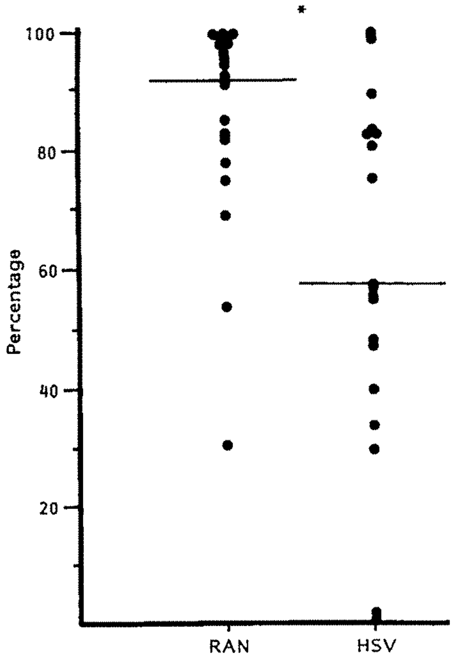


Figure 4 *Night-time* (*midnight–8 am*) *acid suppression after ranitidine 300 mg* nocte (*RAN*) *and after highly selective vagotomy* (*HSV*) *in 20 patients with duodenal ulcer. Lines indicate median suppression.* $^*P<0{\cdot}01$, *RAN* versus *HSV*

was 0·02 mmol/h (quartiles 0–0·41 mmol/h). Most of the vagotomies seem to have been complete; thus our results, in particular the low overnight intragastric pH after HSV, cannot be attributed to incomplete vagotomy.

Other workers who have studied the effects of surgery and drugs on 24 h ambulatory intragastric acidity have measured IGpH by hourly aspiration of small aliquots of gastric juice[8], by continuous nasogastric suction to remove gastric juice in its entirety[9] or by intragastric titration to pH 5·0 with dilute alkali[10]. Direct comparison of our results with the findings of these workers is not valid as any technique involving aspiration of gastric juice, or intragastric titration, will raise antral pH and release gastrin. Thus, discrepancies between our findings and those of others may arise from these methodological differences: aspiration methods of measuring IGpH create an artefactual gastrin stimulus to acid secretion whereas non-aspiration techniques do not. Our technique is unable to measure the volume of acid secreted by the stomach and so acid output cannot be calculated. The non-aspiration techniques, like that described here, minimally disrupt gastric physiology, measure pH every 6 s and are highly reproducible[11] (M. J. Rogers *et al.*, unpublished results) a feature that is poorly documented for other methods of monitoring 24 h ambulatory IGpH.

Using a non-aspiration technique to study 24 h ambulatory intragastric pH in healthy males, Merki *et al.*[12] reported a median 24 h IGpH of 2·5 (quartiles 2·3–3·0) after ranitidine 300 mg at 7 pm. This finding is in good agreement with our observation, median 2·2 (quartiles 1·8–2·7), in patients with duodenal ulcer.

The pattern of intragastric acidity we have observed after ranitidine may have been influenced by the timing of the ranitidine dosage which was given at 10 pm. We used ranitidine 300 mg *nocte* because it is a simple regimen, in widespread clinical use, which has been shown to be as effective in healing duodenal ulcers as a 150 mg b.d. regimen[2]. Since ranitidine has a half-life in plasma of 3 h[13] and its action to suppress acid secretion is of about 4 h duration, a *nocte* dose of ranitidine might be expected to suppress nocturnal acid powerfully, but to provide little suppression of acid after 8 am the next morning. Vagotomy, in contrast, would be expected to give some degree of acid suppression over the entire 24 h period. The median hourly suppression of intragastric acid after HSV and ranitidine (calculated as the reduction in hourly $[H^+]$ by each treatment in each patient) is illustrated in *Figure* 7. Raniditine is seen to provide powerful suppression of acid overnight but little acid suppression after midday next day, whereas HSV affords

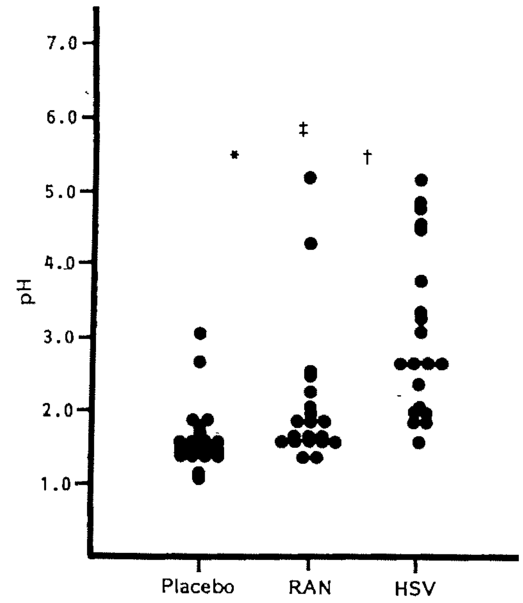


Figure 5 *Median daytime (8 am–midnight) intragastric pH after placebo, ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer.* *P<0·02, *placebo* versus *RAN;* †P<0·001, *RAN* versus *HSV;* ‡P<0·0001, *placebo* versus *HSV*

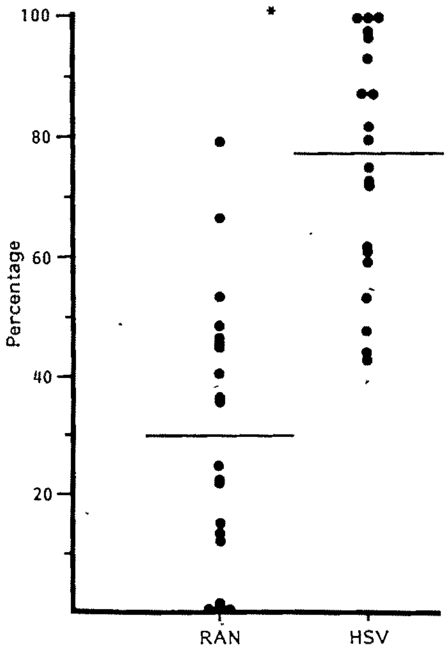


Figure 6 *Daytime (8 am–midnight) acid suppression after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. Lines indicate median acid suppression.* *P<0·0001, *RAN* versus *HSV*

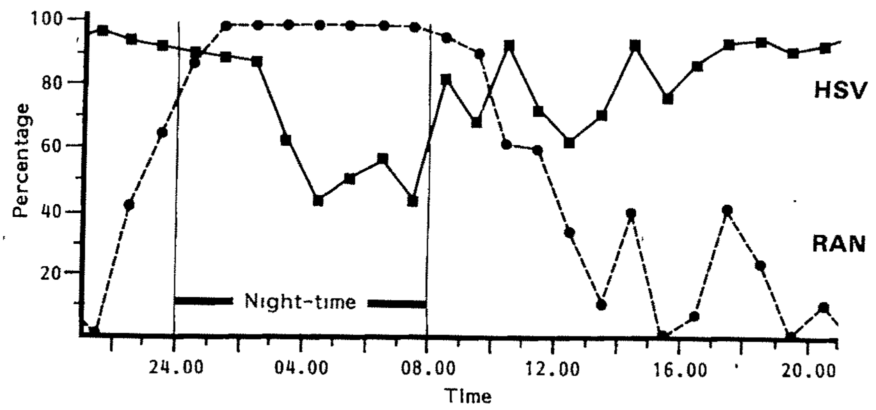


Figure 7 *Median percentage hourly acid suppression seen after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients referred for elective operation for duodenal ulcer. Ranitidine was taken at 10 pm; the night-time period (midnight–8 am) is indicated*

significant inhibition of acid over the entire 24 h, but gives greater suppression of daytime acid than of night-time acid—a finding that is at variance with Dragstedt's[1] ideas about the mode of action of truncal vagotomy.

If suppression of night-time acidity is the *sine qua non* for healing duodenal ulcers, treatments known to be potent in healing duodenal ulcers would be expected to have similar suppressive effects on night-time acid. We have found, however, that HSV and ranitidine gave markedly different degrees of suppression of night-time acidity. Thus the finding that two equally potent ulcer-healing regimens have such disparate effects on night-time acidity constitutes strong evidence against the hypothesis that night-time acidity is of crucial importance.

If powerful suppression of nocturnal acidity is not of critical importance for the healing of duodenal ulcers how can we explain the potent ulcer healing effect of the 300 mg *nocte* ranitidine regimen? Our hypothesis is that inhibition of 24 h intragastric acidity is of fundamental importance in healing duodenal ulcers; H_2 receptor antagonists are more effective in suppressing nocturnal acidity than daytime acidity, but they heal duodenal ulcers via their effect on 24 h acidity HSV is more effective in suppressing daytime acidity than night-time acidity but its ulcer healing effect relates to its effect on 24 h acidity.

In summary, we have found that, contrary to Dragstedt's teaching[1], vagotomy suppresses daytime acidity more effectively than night-time acidity. Furthermore, the disparate effects of ranitidine and HSV on night-time acidity contrasts with their similar effect in healing duodenal ulcers. Hence, suppression of nocturnal acidity is not of major importance in the healing of duodenal ulcers.

References

1. Dragstedt LR, Owens FM. Supra-diaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc Soc Exp Biol Med* 1943; **53**: 152–4
2. Ireland A, Colin-Jones JG, Gear P *et al.* Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984, **ii**: 274–6.
3. Colson RH, Watson BW, Fairclough PD *et al.* An accurate, long-term, pH-sensitive radio pill for ingestion and implantation *Biotelemetry Patient Monitoring* 1981; **8** 213–27
4. Rogers MJ, Holmfield JHM. A simple method for reducing signal loss from intragastric radiotelemetry capsules *Surg Res Comm* 1988; **4**: 171–6.
5. Johnston D, Wilkinson AR, Humphrey CS *et al.* Serial studies of gastric secretion in patients after highly selective (parietal cell) vagotomy without a drainage procedure for duodenal ulcer II. The insulin test after highly selective vagotomy *Gastroenterology* 1973; **64**. 12–21
6. Cohen L, Halliday M *Statistics for Social Scientists*, 1st edn. London. Harper and Row, 1982.
7. Hollander F Laboratory procedures in the study of vagotomy (with particular reference to the insulin test) *Gastroenterology* 1948, **11**: 419–25.
8. Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ Effect of cimetidine on 24-h intragastric acidity in normal subjects. *Gut* 1976, **17**: 133–8
9. Gledhill T, Buck M, Paul A, Hunt RH Cimetidine or vagotomy? Comparison of the effects of proximal gastric vagotomy, cimetidine and placebo on nocturnal intragastric acidity in patients with cimetidine resistant duodenal ulcer. *Br J Surg* 1983; **70** 704–6
10. Feldman M, Richardson CT. Total 24-hour gastric acid secretion in patients with duodenal ulcer. *Gastroenterology* 1986; **90** 540–4.
11. Merki HS, Witzel L, Walt RP *et al.* Day-to-day variation of 24-hour intragastric acidity. *Gastroenterology* 1988; **94**· 887–91
12. Merki HS, Witzel L, Walt RP *et al* Double blind comparison of the effects of cimetidine, ranitidine, famotidine and placebo on intragastric acidity in 30 normal volunteers *Gut* 1988, **29** 81–4
13. Martin LE, Bell JA, Carey PF *et al.* A review of pharmacokinetics and metabolism of ranitidine in animals and man. In Misiewicz JJ, Wormsley KG, eds *The Clinical Use of Ranitidine*, 1st edn Oxford. The Medicine Publishing Foundation, 1981· 23–31
14. Caulin C, Isal JP, Alexandre C *et al* Correlation between intragastric pH and plasma ranitidine concentrations In: Misiewicz JJ, Wormsley KG, eds *The Clinical Use of Ranitidine*, 1st edn. Oxford. The Medicine Publishing Foundation, 1981· 114–18.

Br. J. Surg. 1988, Vol. 75, October, 966–968

Surgical glove perforation

R. D. A. Dodds, P. J. Guy, A. M. Peacock*, S. R. Duffy, S. G. E. Barker and M. H. Thomas

*Departments of Surgery and *Microbiology, St. Peter's Hospital, Guildford Road, Chertsey, Surrey KT16 0PZ, UK*

Correspondence to:
Mr M. H. Thomas

In a study to investigate the incidence and significance of surgical glove perforation, bacterial contamination of surgeons' hands and gloves before and after operation was measured and the gloves tested for damage. Perforations were found in 74 of 582 gloves (12·7 per cent) and occurred in 34·5 per cent of operations. Glove perforation did not influence bacterial counts on the surgeons' hands or on the outside of their gloves. A separate clinical study of 100 adult hernia repairs gave no evidence that perforation increased wound sepsis. After standard pre-operative hand preparation, glove perforations are of no clinical significance to the patient, but their high incidence should alert surgeons to the need for protection against pathogens transmissible during surgery, such as hepatitis B and the human immunodeficiency virus. Protection of the surgeon is the main indication for peroperative change of damaged gloves.

Keywords: Surgical gloves, HIV transmission, wound infection

The surgical glove was introduced in 1889 by Halsted to protect his nurse assistant, Caroline Hampton, from dermatitis caused by mercuric chloride used for Listerian antisepsis. It was soon realized that sterile gloves provided a barrier between the surgeons' hands and the patient and could thus reduce iatrogenic infection. Lord Moynihan pioneered their use in the UK and the wearing of gloves during surgery has long been standard practice.

Modern surgical scrub technique dramatically reduces the bacterial counts on surgeons' hands, although some organisms remain[1,2]. It has often been stated that when glove perforation occurs, bacteria can escape and contaminate the wound, thus leading to an increased risk of wound sepsis[3–5]. For this reason surgeons change their gloves during an operation when perforation has occurred although supporting bacteriological evidence is scant[6]. In this study we measured the bacterial contamination of surgeons' hands and gloves before and after surgery and observed the effect of glove perforation on the bacterial counts. In addition we assessed in a separate study the influence of glove perforation on clinical wound sepsis rate after hernia repair.

Patients and methods

The hands and gloves of personnel undertaking clean or clean contaminated[7] general surgical operations were studied on 100 occasions (57 surgeons and 43 assistants). After pre-operative hand preparation the residual bacterial contamination was assessed. Immediately at the end of the operation, before any further contamination, the procedure was repeated for the outside of the gloves and the ungloved hands. The gloves were then tested for perforations. Hand bacterial contamination was similarly assessed in 60 control hands not subjected to a surgical scrub technique.

Washings were obtained for bacteriological examination by the method of Casewell *et al.*[8], after Salzman *et al.*[9]. The investigator 'scrubbed' and gloved in the usual way before obtaining samples. Using an aseptic technique, 50 ml aliquots of Ringer lactate solution were placed in a pair of size 9 Biogel gloves (Regent Dispo, LRC Products Ltd., London). With the aid of the gloved investigator the surgeon placed both his prepared hands into the sampling gloves, and agitated the solution by vigorous intermittent flexing of the fingers and shaking of the hands for 1 min. The glove was removed from the hand by the investigator and the contents poured into a sterile container. Following surgery, the procedure was repeated first on the outside of the gloves and then again on the ungloved hands. Neutralizing agents were not employed as the samples were transported directly to the laboratory for immediate culture. After ensuring adequate mixing of the specimens, 50 μl aliquots of solution were placed on a Colombia blood agar plate (Difco Laboratories), dried and incubated for 24 h at 37°C. The number of colony-forming units from the two aliquots was read from the plates by the same microbiologist and the average count expressed as the number of colony-forming units per millilitre of sampling solution (c.f.u./ml). The upper limit of resolution of the method is 10 000 c.f.u./ml.

After the samples had been obtained the integrity of the gloves was tested by filling them under pressure with tap water. The addition of methylene blue allowed easier identification of any puncture. The same test was performed on 430 unused Biogel gloves. Information was recorded on a standard proforma documenting the site and type of glove perforation and whether the surgeon had been aware of any damage to the glove.

In the second part of the study the gloves of surgeon and assistant in 100 consecutive adult inguinal or femoral hernia repairs were tested for the presence and type of perforation. The wounds were then observed between 7 and 10 days postoperatively for signs of infection. No prophylactic antibiotic therapy was used.

Results

Incidence and type of glove perforation

A total of 582 surgical gloves were tested and 74 perforations found, an overall incidence of 12·7 per cent. One or more perforations were present in 34·5 per cent of operations. Damage was found in 48 of 314 (15·3 per cent) principal surgeons' gloves and in 26 of 268 (9·7 per cent) assistants' gloves. All the personnel were right-handed. Of the 48 perforations in the principal surgeons' gloves, 39 were in the left glove (81 per cent) while only 16 of the 26 (62 per cent) perforations in the assistants' gloves were in the left glove. In 85 per cent of cases the perforation was a needle prick as opposed to a glove tear and in 50 per cent the operator was unaware that perforation had occurred. Of the 430 unused surgical gloves, 13 (3 per cent) were found to contain perforations.

Effect of glove perforation on bacterial contamination

The mean bacterial contamination measured on 60 unwashed hands was 1754 c.f.u./ml compared with 58 c.f.u./ml on the scrubbed hands before surgery. Bacteriological studies were undertaken in 200 washed hands and 200 gloves. A perforation was demonstrated in 37 of the 200 surgical gloves. The distribution of bacterial counts on the pre-operative scrubbed hands, postoperative gloves and postoperative hands are summarized in *Figure 1*. The values are skewed towards the zero and do not allow direct statistical comparison. Nevertheless the pattern of distribution of bacterial counts is similar whether perforation has occurred or not.

0007–1323/88/100966–03$3.00

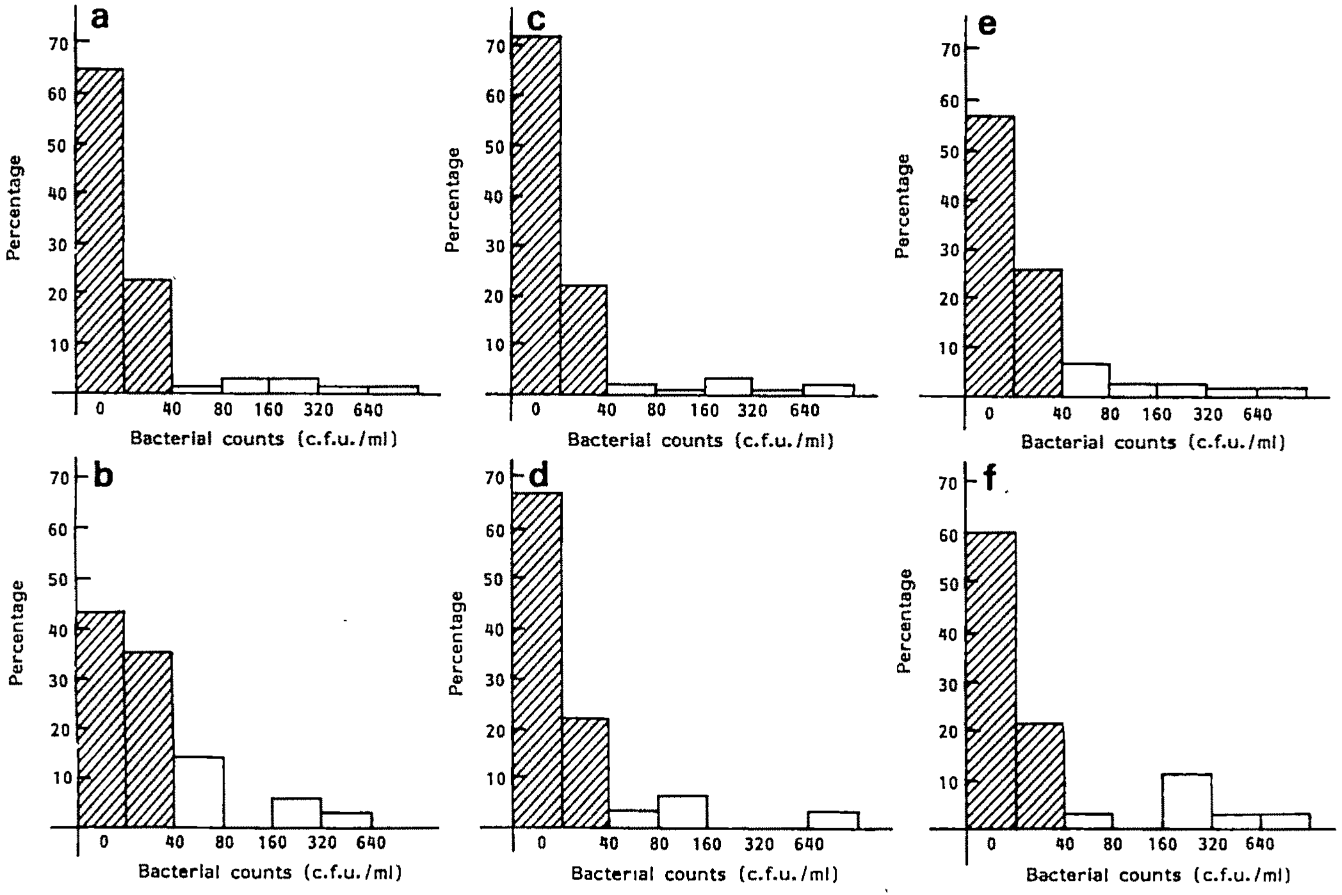


Figure 1 *Distribution of bacterial counts on* **a** *the surgeon's hands after scrubbing, gloves intact* (n=*163*); **b** *the surgeon's hands after scrubbing, gloves perforated* (n=*37*), **c** *the outside of the gloves postoperatively, gloves intact* (n=*163*), **d** *the outside of gloves postoperatively, gloves perforated* (n=*37*), **e** *the surgeon's hands postoperatively, gloves intact* (n=*163*), **f** *the surgeon's hands postoperatively, gloves perforated* (n=*37*) *The hatched area represents clean hands* (**a**, **b**, **d**, **e**) *or clean gloves* (**c**, **d**) (*≤40 c.f.u./ml*). *c.f.u., Colony-forming units per millilitre of sampling solution*

Hands or gloves that grew ≤40 c.f.u./ml were designated in this analysis as 'clean' while those that gres >40 c.f.u./ml were designated 'dirty'. After scrubbing, 87 per cent of hands grew ≤40 c.f.u./ml and were therefore 'clean'. All the gloves were considered clean before surgery. The state of the hands (clean or dirty) before and after surgery is summarized in *Table 1* and that for gloves in *Table 2*. Glove perforation produced no change in the proportion of dirty hands or gloves at the end of surgery.

In order to isolate the effect of glove perforation on bacterial contamination we analysed the 27 cases in which one of a pair of gloves was perforated. The two hands were therefore matched in all respects apart from the presence of perforation. This pairing and matching allowed for all other variables such as pre-operative hand preparation, type of operation and length of procedure. Change from clean pre-surgery to dirty post-surgery was examined. The results are summarized in *Table 3*. McNemar's test of association yielded a significance value of $P = 0.62$ for hands and $P = 0.5$ for gloves. There is therefore no evidence from these data to suggest that a change of clean hands or gloves pre-surgery to dirty post-surgery was more likely when a glove was perforated.

Effect of glove perforation on the incidence of wound sepsis

The results from the clinical study of 100 consecutive adult hernia repairs are expressed in *Table 4*. The Fisher–Irwin exact significance test was applied ($P = 0.75$, two-tailed test) and showed no evidence of an association between glove perforation and postoperative clinical wound sepsis.

Discussion

Perforation of the surgical glove is a common event. Our operative perforation rate of 34·5 per cent accords with other surveys[3,10,11]. We found that the surgeon is only aware that perforation has occurred on half the occasions, indeed 3 per cent of gloves donned are perforated before the operation starts.

As the principal surgeon uses the sharp instruments such as scalpel and needle with his dominant hand, it is not surprising that the majority of perforations occur in his non-dominant glove, particularly the index and middle finger tips. There was a lower incidence and more random distribution for perforation in the assistants' gloves.

Our bacteriological study confirms that scrubbing significantly reduces hand bacterial counts and shows that glove perforations do not increase the bacterial contamination on the outside of the surgeons' gloves or his hands The second study demonstrates that perforations do not increase the risk of clinical wound sepsis. Following the use of modern antibacterial surgical scrub preparations it is the non-pathogenic resident skin flora such as *Staphylococcus epidermidis*, often associated with skin squames, that remain on the surgeons' hands[1,12]. This organism has been implicated in infections on prosthetic heart valves[13]. The removal of the pathogenic transient skin flora such as *Staphylococcus aureus* and as many of the resident bacteria as possible is probably more important than the wearing of surgical gloves in preventing iatrogenic sepsis. Although no studies have been carried out on general surgical operations performed ungloved, suturing without gloves of wounds in an accident department has been shown not to increase wound sepsis[14]. Transfer of hepatitis B virus between surgeon and patient has occurred, but it is not certain to what extent glove perforation was implicated[15].

Although the surgeons' hand bacteria may pass out through a glove perforation, organisms, blood and other substances can also pass into a perforated glove, perhaps by a sucking action. All surgeons have noticed blood on their fingers after an operation when a glove has been damaged. While intact surgical

Table 1 *Contamination of surgeons' hands* (n = 200) *related to glove perforation*

	Before surgery	After surgery	
		Perforation	Intact
Clean (⩽40 c.f.u./ml)	87%	81%	83%
Dirty (>40 c.f.u./ml)	13%	19%	17%

c.f.u., colony-forming units per millilitre of sampling solution

Table 2 *Contamination of surgeons' gloves* (n = 200) *related to glove perforation*

	Before surgery	After surgery	
		Perforation	Intact
Clean (⩽40 c.f.u./ml)	100%	89%	92·5%
Dirty (>40 c.f.u./ml)	0%	11%	7·5%

c.f.u., colony-forming units per millilitre of sampling solution

Table 3 *Change of bacterial contamination for the 27 matched pairs of hands and gloves in which one of the pair of gloves was perforated*

	Intact glove: change from clean* (pre-op.) to dirty† (post-op.)		
	Yes	No	Total
Hands			
Perforated glove: change from clean* (pre-op.) to dirty† (post-op.)			
Yes	2	1	3
No	3	21	24
Total	5	22	27
Gloves			
Perforated glove. change from clean* (pre-op.) to dirty† (post-op.)			
Yes	1	1	2
No	1	24	25
Total	2	25	27

* Clean, ⩽40 colony-forming units per millilitre of sampling solution, † dirty, >40 colony-forming units per millilitre of sampling solution

Table 4 *Relationship of glove perforation to wound infection in 100 patients*

	Glove perforation		
	Present	Absent	Total number of patients
Wound infection			
Present	4	6	10
Absent	27	63	90
Total number of patients	31	69	100

gloves are impermeable to the human immunodeficiency virus (HIV)[16], perforated gloves are not. We suggest that Halsted's original reason for introducing the surgical glove, to protect the operator, attains a new pertinence. With adequate preoperative hand preparation there is no risk to the patient from surgical glove perforation. Protection of the surgeon is the main indication for a peroperative change of damaged gloves.

The growing number of HIV-positive patients poses a threat to the surgeon today. He cannot rely on the integrity of his gloves; some are perforated before being donned and many more are damaged during surgery. Half the glove perforations remained undetected. Sim and Dudley recently stated that to protect ourselves we should re-examine the basic techniques we use[17], the results of our study strongly support this action.

Acknowledgements

We acknowledge the assistance of Mrs N. Machonochie with the statistics and of L R.C. Products Ltd for supplying the materials.

References

1. Ayliffe GAJ Surgical scrub and skin disinfection. *Infection Control* 1984; **5**: 23–7.
2. Lowbury EJL, Lilly HA, Bull JP Disinfection of hands removal of resident bacteria. *Br Med J* 1963; **i**: 1251–6.
3. Devenish EA, Miles AA. Control of *Staphylococcus aureus* in an operating theatre. *Lancet* 1939; **i**: 1088–94
4. Smylie HG, Webster CU. 'Phisohex' and safer surgery. *Br Med J* 1959; **ii**: 606–9.
5. Lowbury EJL, Lilly HA. Disinfection of the hands of surgeons and nurses. *Br Med J* 1960; **i**. 1445–50.
6. Davidson AIG, Smith G, Smylie HG. A bacteriological study of the immediate environment of a surgical wound. *Br J Surg* 1971; **58**: 326–33.
7. Cruse PJ, Foord R. A five year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; **107**: 206–10.
8. Casewell MW, Dalton MT, Webster M, Phillips I. Gentamicin resistant *Klebsiella aerogenes* in a urological ward. *Lancet* 1977; **ii**: 444–6.
9. Salzman TC, Clark JJ, Klemm L. *Proceedings of the 7th Inter-Science Conference on Antimicrobial Agents and Chemotherapy*. Washington DC: American Society for Microbiology, 1967: 97.
10. Church J, Sanderson P. Surgical glove punctures (letter) *J Hosp Infect* 1980; **1**: 84.
11. O'Connor AG Glove puncture during operation. *Nursing Times* 1984, **80**, Suppl: 5–6.
12. Price PB The bacteriology of normal skin: a new quantitative test applied to a study of the bacterial flora and the disinfectant action of mechanical cleaning. *J Infect Dis* 1938; **63**: 301–18.
13. Van Den Broek PJ, Lampe AS, Berbée GAM *et al.* Epidemic of prosthetic valve endocarditis caused by *Staphylococcus epidermidis*. *Br Med J (Clin Res)* 1985; **291**: 949–50
14. Bodwala GC, George TK. Surgical gloves during wound repair in the accident and emergency department. *Lancet* 1982; **ii**: 91–2
15. Collaborative Study. Acute hepatitis B associated with gynaecological surgery. *Lancet* 1980; **i** 1–6.
16. Dalgleish AG, Malkovsky M. Surgical gloves as a mechanical barrier against human immunodeficiency viruses. *Br J Surg* 1988; **75**: 171–2.
17. Sim AJW, Dudley HAF Surgeons and HIV. *Br Med J* 1988; **296**: 80.

Br. J. Surg. 1988, Vol. 75, October,
969–971

Comparison of absorbable materials for surgical haemostasis

S. D. Blair,
C. M. Backhouse,
R. Harper,
J. Matthews and
C. N. McCollum

Department of Surgery, Charing Cross and Westminster Medical School, London W6, UK

Correspondence to:
Mr S. D. Blair, Department of Surgery, Charing Cross and Westminster Medical School,
St Dunstan's Road,
London W6 8RP, UK

The haemostatic effect of two new materials has been compared with surgical gauze and oxidized cellulose using a standardized liver laceration in New Zealand White rabbits. Following excision of a 3 cm^2 disc of tissue from the liver, 42 rabbits were randomized to the use of gauze swabs (n = *6*)*, oxidized cellulose* (*Surgicel*®) (n = *12*)*, porcine collagen* (*Medistat*®) (n = *12*) *or calcium alginate* (*Kaltostat*®) (n = *12*) *to control the resulting haemorrhage. Blood loss and time to haemostasis were accurately recorded. The absorbable materials were left* in situ *and animals killed between 2 weeks and 6 months later to examine speed of absorption and resulting adhesions. Calcium alginate stopped bleeding in <3 min in all animals compared with a mean* (±*s.e.m.*) *of $5{\cdot}7 \pm 0{\cdot}75$ min for porcine collagen, $12{\cdot}5 \pm 0{\cdot}9$ min for oxidized cellulose and >15 min with gauze* ($P < 0{\cdot}001$)*. Oxidized cellulose and calcium alginate reabsorbed within 3 months leaving a fibrous scar, but a vigorous foreign body reaction was seen with porcine collagen which caused intestinal obstruction in 5 out of 12 animals within 3 months.*

Keywords: Haemostasis, oxidized cellulose, porcine collagen, calcium alginate

The control of haemorrhage is an essential part of any operation but is particularly difficult following laceration or surgical incision of parenchymatous organs such as the liver or spleen. Ligature may be used for larger arteries or veins with diathermy for smaller vessels but widespread oozing is difficult to control.

We studied the haemostatic action of two new materials designed to stimulate platelet aggregation or blood coagulation and compared them with existing materials. Medistat (Genetic Laboratories), a new formulation of porcine collagen in a macrofibrillar sponge, has been recommended for surgical haemostasis as collagen potently activates platelet aggregation[1]. Kaltostat (BritCair Limited) contains calcium alginate fibres which release calcium ions on contact with blood; the increased local calcium concentration stimulates rapid coagulation. This calcium is exchanged for sodium ions from plasma which form sodium alginate, a gel that is readily absorbable and prevents the material adhering[2,3]. For comparison, simple gauze swabs and oxidized cellulose (Surgicel, Johnson and Johnson Limited), both of which stimulate platelet and blood coagulation by contact activation alone, were also studied using the same model of liver laceration[4,5].

Materials and methods

Under general anaesthesia a standard 3 cm^2 liver wound was made in 42 New Zealand White rabbits by pressing a metal template firmly onto the liver and excising the protruding tissue with a scalpel. Gauze or haemostatic material was immediately applied under gentle pressure according to a randomization code, with 6 animals having standard surgical gauze applied and 12 each using one of the three haemostatic materials: oxidized cellulose (Surgicel), porcine collagen (Medistat) or calcium alginate (Kaltostat).

Measurement of bleeding

The wound was inspected at 3-min intervals for up to 18 min and the time to complete haemostasis recorded. Blood loss was accurately measured by carefully packing off the wound area and washing all swabs used in 1 litre of heparinized saline. The red cells in a 20 ml sample were then haemolysed by adding potassium cyanide and the resulting haemoglobin concentration measured in a Coulter haemoglobinometer. Total blood loss was calculated by comparing this haemoglobin concentration with a similar preparation of 2 ml of the rabbit's blood taken at operation, diluted and prepared in the same way.

Rate of absorption of material left in situ

Half of the 42 rabbits were killed at 2 weeks and the remaining 21 animals at 6 weeks. An additional 12 rabbits were studied in which each of the three different test materials were placed at marked sites on both the liver surface and in the small bowel mesentery. These 12 animals were then killed in batches of three at 3, 4, 5 and 6 months. The macroscopic appearance of the material, the surrounding fibrous response and the influence on the abdominal organs were then examined with particular attention to adhesion formation. The microscopic appearance of each specimen was then classified as to whether there was

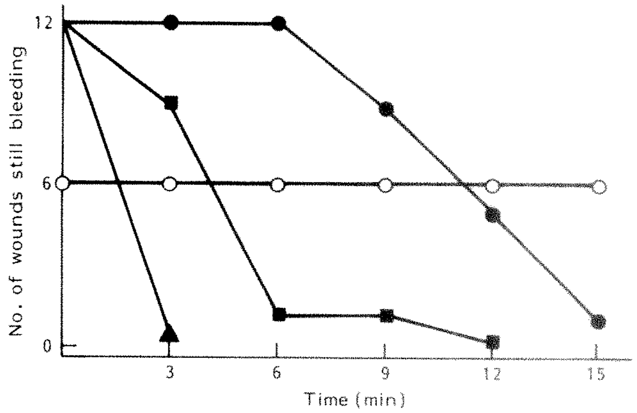


Figure 1 *Effect of the different materials on time to haemostasis. The standardized liver laceration was inspected at 3-min intervals and the time when bleeding ceased recorded. None stopped within 18 min with surgical gauze. Haemostasis was achieved at between 6 and 15 min with oxidized cellulose and between 3 and 6 min with porcine collagen. Calcium alginate stopped bleeding within 3 min in all animals.* ○, *Surgical swabs* (n = *6*)*;* ▲, *calcium alginate* (n = *12*)*;* ■, *porcine collagen* (n = *12*)*;* ●, *oxidized cellulose* (n = *12*)

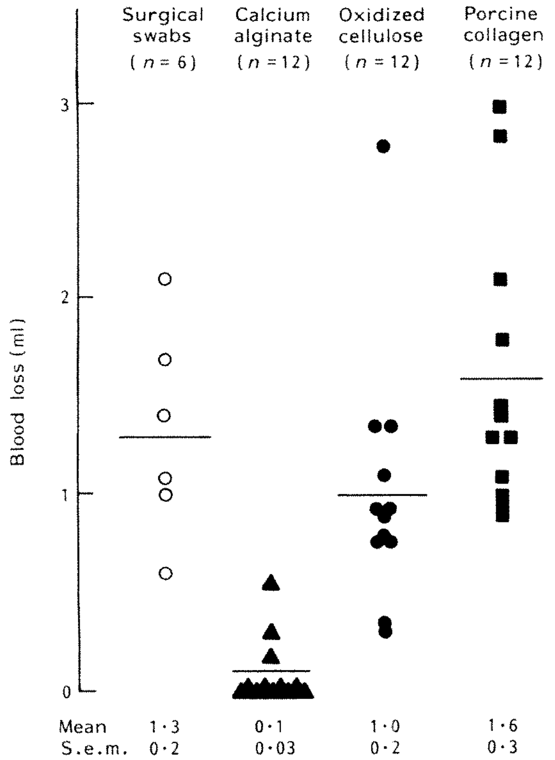


Figure 2 *Effect of the different materials on amount of blood loss. Although gentle pressure was applied to all materials, the resulting blood loss was significantly less with calcium alginate* ($P < 0{\cdot}01$)

residual material, the degree of fibrosis and the presence of foreign body reaction.

Results

The standardized liver laceration consistently resulted in profuse small vessel bleeding from the cut surface which could not be stopped in under 18 min, despite pressure in any of the animals randomized to application of surgical gauze. In contrast, calcium alginate stopped bleeding within 3 min in every animal randomized to application of this material (*Figure 1*). Both porcine collagen and oxidized cellulose were significantly more effective than surgical gauze but took longer to stop the bleeding than calcium alginate, with mean times to haemostasis of 5·7 ± 0·75 and 12·5 ± 0·9 min respectively ($P < 0{\cdot}001$; Mann–Whitney *U* test). In the six wounds that continued bleeding after 18 min despite the application of surgical gauze under local pressure, bleeding stopped with application of calcium alginate within 3 min in each case. As there was doubt as to whether macrofibrillary porcine collagen could be absorbed, collagen was removed 10 min after haemostasis had been obtained in half the animals in this group. In every case, profuse haemorrhage restarted immediately the coagulum was dislodged and fresh collagen had to be applied.

Mean blood loss with surgical gauze application was 1·3 ± 0·2 ml and was only significantly reduced by calcium alginate to 0·1 ± 0·03 ml ($P < 0{\cdot}01$) (*Figure 2*). There was no significant difference in blood loss between animals with gauze application and the other two haemostatic materials, but direct pressure was applied to prevent further bleeding, as the rabbits would have become too ill to continue the study.

On examination of the liver laceration site after death

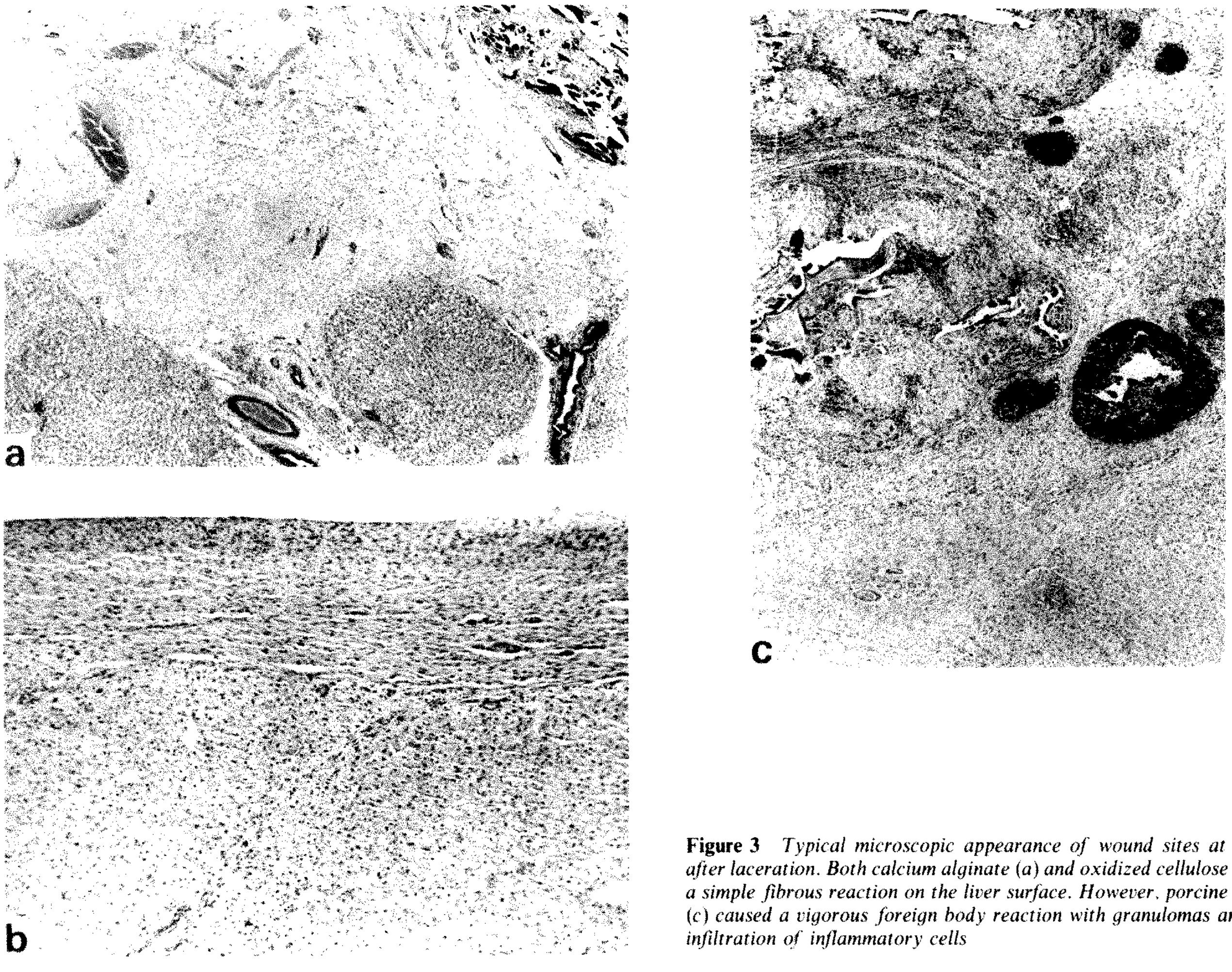


Figure 3 *Typical microscopic appearance of wound sites at 6 weeks after laceration. Both calcium alginate* (*a*) *and oxidized cellulose* (*b*) *show a simple fibrous reaction on the liver surface. However, porcine collagen* (*c*) *caused a vigorous foreign body reaction with granulomas and heavy infiltration of inflammatory cells*

at 2 weeks, the haemostatic materials left *in situ* were surrounded by an inflammatory mass irrespective of the agent used. By 6 weeks, the inflammatory mass had resolved in all wounds treated with calcium alginate and oxidized cellulose, leaving a local fibrous scar with fibrinous omental adhesions. In the collagen group, an inflammatory mass was still present in two out of six wounds. Microscopically, where calcium alginate and oxidized cellulose had been implanted, healing was by fibrosis with gradual reabsorption of the material. Porcine collagen was surrounded by a granulomatous foreign body reaction in two out of six animals at 2 weeks, and in all animals by 6 weeks (*Figure 3*).

In the 12 additional animals where all three haemostatic materials were left *in situ* on the liver and small bowel mesentery, five died during the first 2 months with small bowel obstruction from adhesions produced around porcine collagen. Of the remaining seven animals, two were killed at 3, 4 and 6 months and the remaining one at 5 months. Five out of these seven animals had omental adhesions, three to sites of oxidized cellulose and two to porcine collagen. Although calcium alginate was completely reabsorbed at 4 and 5 months, residual calcification could be identified at four of the relevant six sites. By 6 months, the remaining four implantation sites for both calcium alginate and oxidized cellulose were free of calcification.

Discussion

Calcium alginate was significantly better at stopping haemorrhage from this experimental liver laceration than surgical gauze, porcine collagen or the existing haemostatic material, oxidized cellulose. On follow-up in animals where these materials had been left *in situ*, both oxidized cellulose and calcium alginate were completely absorbed without complication. Foreign body granulomata were consistently found around porcine collagen and led to fatal small bowel obstruction in nearly half the animals where collagen had been placed in the small bowel mesentery. In addition, as removing collagen dislodges the haemostatic coagulum and rebleeding usually follows, this form of collagen cannot be recommended as a haemostatic agent. Where collagen has been shown previously to be more haemostatic than oxidized cellulose, microcrystalline bovine collagen was used and no granuloma formation was then seen[6,7]. Calcium alginate has not previously been compared with other topical haemostatic agents, although it has been reported to reduce blood loss from skin graft donor sites[8]. Furthermore, in experimental skin wounds where calcium alginate was left in the wounds, it was quickly absorbed and did not interfere with normal healing[9].

Calcium alginate is a naturally occurring polysaccharide that may be manufactured at considerably less cost than any of the other topical haemostatic agents currently available. As it is cheap, it may have potentially wide application throughout surgery; not only for uncontrolled haemorrhage from the liver or spleen, but wherever bleeding or 'oozing' is encountered from areas of raw tissue such as the space following rectal mobilization, the gallbladder bed or flaps at mastectomy. In this situation, the sodium alginate gel which forms following calcium ion exchange becomes important as it allows the material to be removed without dislodging the fragile new coagulum. Further clinical studies are planned to assess the effect of this material on operative blood loss.

References

1. Mason PG, Pead MS. Some effects of a microcrystalline collagen preparation on blood. *Haemostasis* 1974, **3**. 31
2. Blaine G. Experimental observations on absorbable alginate products in surgery. *Ann Surg* 1947, **125**: 102–14
3. Jarvis PM, Galvin DAJ, Blair SD, McCollum CN How does calcium alginate achieve haemostasis in surgery? *Thromb Haemostas* 1987; **58**: 50.
4. Frantz VK, Clarke HT, Lattes R. Haemostasis with absorbable gauze (oxidised cellulose). *Ann Surg* 1944, **120**: 181–98.
5. Hurwitt ES, Henderson J, Lord GH, Gitlitz GF, Lebendiger A A new surgical absorbable haemostatic agent. *Am J Surg* 1960, **100**: 439–46
6. Abbott WM, Austen WG. The effectiveness and mechanism of collagen induced topical haemostasis *Surgery* 1975, **78** 723–9.
7. Hait MR, Robb CA, Baxter GR. Comparative evaluation of avitene microcrystalline collagen hemostat in experimental liver wounds. *Am J Surg* 1973; **125** 284–7.
8. Groves AR, Lawrence JC. Alginate dressing as a donor site haemostat. *Ann R Coll Surg* 1986, **68** 27–8
9. Barrett SE, Varley SJ The effects of calcium alginate on wound healing. *Ann R Coll Surg* 1987; **69** 153–5

Br. J. Surg. 1988, Vol. 75, October,
972–975

Endocrine basis for the clinical presentation of hidradenitis suppurativa

B. J. Harrison,
G. F. Read* and
L. E. Hughes

Department of Surgery,
University of Wales College of
*Medicine and * Tenovus Institute,*
Heath Park, Cardiff
Correspondence to:
Professor L. E Hughes,
Department of Surgery, University
of Wales College of Medicine,
Heath Park, Cardiff CF4 4XN, UK

Clinical assessment of 134 patients with hidradenitis suppurativa revealed clinical evidence supporting an androgen-based endocrine disorder underlying the condition. Such features included postpubertal onset maximal during the third decade; female preponderance (13:5); premenstrual flare in 57 per cent of women; absence of this flare associated with irregular or anovulatory menstrual cycles; and an increased incidence of obesity and acne. Detailed hormone profiles in 36 female patients and 14 controls showed evidence of relative androgen excess and decreased progesterone levels in those patients without a premenstrual flare. Obesity and enhanced peripheral androgen conversion by apocrine tissue are possible explanations for normal serum androgen profiles in patients with a flare. Precise elucidation of the hormonal abnormality is a prerequisite for effective medical treatment of early disease.

Keywords: Sweat gland diseases, androgens

Hidradenitis suppurativa is a condition causing very severe morbidity, and for which no entirely satisfactory treatment exists. The association between the clinical features of hidradenitis suppurativa, 'physiological' hormonal events (such as puberty[1], pregnancy[2] and the menstrual cycle[3]), and overt endocrine disorders[4,5] has led for many years to speculation that hormonal factors are involved in the disease. We[6] and subsequently several other groups[7,8] have now reported findings sufficient to label hidradenitis as a cutaneous manifestation of variably expressed androgen excess, and have provided a rationale for the treatment of early disease with cyproterone acetate[9]. While the most detailed of these studies[7] reported clinical and biochemical data from 42 women with hidradenitis, the authors did not elaborate on the mechanisms by which the abnormal milieu might account for the clinical manifestations of the disease. Characterization of a specific endocrine abnormality could lead to effective medical treatment in the early stages and avoid the extensive surgery necessary to relieve the established disease.

We have now examined specific clinical and biochemical features in a large series of patients, female and male, to assess the relationship between the clinical presentation of hidradenitis and the putative underlying endocrine (androgen) disorder. The clinical and endocrine studies constitute two separate but inter-related studies. The clinical evidence obtained from the first study guided the direction of the biochemical study in an attempt to elucidate the endocrine basis for the disorder.

Patients and methods

Clinical study

The case records of 152 patients with hidradenitis referred to the University Department of Surgery between 1978 and 1986 were examined. Of these patients, 130 were interviewed by the first author at a designated review clinic or on admission to hospital before surgery. Of the 22 patients not reviewed, one was known to have died of an unrelated cause (malignant melanoma) and four returned a postal questionnaire Seventeen patients remained untraced Some patients, particularly those with very long histories, were unable to provide precise responses to all questions.

Age at onset (*110 patients*). This was defined as the age at which hidradenitis—'recurrent boils or abscesses'—first occurred at a typical site, namely axillary, inguinoperineal, perianal, or mammary skin.

Gynaecological and obstetric features. Eighty-seven women were questioned about their menstrual history and about whether or not they had noticed an alteration in disease activity during the menstrual cycle or in pregnancy. Criteria used to designate menstrual cycles as 'regular' (25–31 days) or 'irregular' (<25 >31 days) were obtained from the study by Chiazze *et al*[10].

Sites involved. Details were derived from information recorded in the hospital records of 146 patients and where possible confirmed at the 130 follow-up interviews.

Body mass index. Weight in kg/(height in metres)^2 was used as an index of obesity. Measurements were recorded with patients wearing normal indoor clothing as recommended on the field procedures of the Office of Population Census and Surveys social survey division report[11]. Body mass index (BMI) <20 was regarded as underweight, 25–30 as overweight and >30 as obese. Control values for men and women were obtained from the Office of Population Census and Surveys' data for BMI distribution in Wales.

Acne. This was defined as present if equivalent to acne minor or 'clinical' acne grades 2–10 as described elsewhere[12]

Hormonal study

Peripheral venous blood samples were obtained from 36 female patients (mean age ± s d , 31·2 ± 8 years) and 14 controls (28 5 ± 9 years). Patients with hidradenitis were classified according to whether they experienced premenstrual exacerbation of disease into 'flare' and 'no flare' groups. Individuals taking anti-hypertensives or tranquillizers, and those with known endocrine disorders, were excluded. Other exclusion criteria included history or signs of severe acne/hirsutes, severe menstrual disorder (cycle length <15 or >45 days), or infertility. Use of the contraceptive pill also rendered patients and controls ineligible. All women were tested during the premenstrual phase of their cycles. Sampling was performed between 09 00 and 13.00 hours with patients after a standard rest period of 15 min. Blood (20 ml) was withdrawn from an antecubital fossa vein, the serum separated and then stored at −20°C All steroid hormone assays were performed within the Tenovus Institute Laboratories, Cardiff, UK Testosterone (normal range 0 3–2·5 nmol/l) and dehydroepiandrosterone sulphate were measured as described elsewhere[13,14]. Androstenedione (normal range 0·6–8 8 nmol/l) was assayed using an in-house extraction magnetic radioimmunoassay technique. Serum 17β-oestradiol and progesterone were measured using commercially available kits from Steranti Research Ltd. (St. Albans, UK) and Diagnostic Products Corporation (Los Angeles, USA). Sex-hormone-binding globulin assays[15] were kindly performed by Colin Selby in the Department of

Table 1 *Age at onset of hidradenitis in 35 men and 75 women*

Age (years)	Men (n)	Women (n)	Total (%)
0–10	1	3	3·6
11–20	9	17	23·6
21–30	13	34	42·7
31–40	12	15	24·5
41–50	—	5	4·5
50+	—	1	<1
Mean age ± s.d.	24·5±9	24·9 ± 10	
Median	25	23	
Range	<1–35	1–50	

Clinical Biochemistry, Nottingham City Hospital. All assays were set up in batches after a single freeze/thaw cycle with appropriate standards and control sera. Inter- and intra-assay variations were less than 10 per cent. The androgen index for each individual was calculated using the formula: androgen index = (testosterone/sex hormone-binding globulin) × 100.

Statistical analysis

Distribution-free methods were used for analysis of data with skewed distribution or possible non-normality when sample sizes were too small to establish normality Fisher's exact test was used for the comparison of the frequency of observations with small numbers

Results

Clinical study

A total of 109 women and 43 men with hidradenitis were referred to the University Department of Surgery over the 8-year period under study.

Age at onset (*Table 1*). Hidradenitis was predominantly a disease of the period of sexual endocrine activity. Onset within the first decade occurred in only four patients, aged 6 months, 1, 3 and 9 years respectively. Maximal onset was observed during the third decade in both sexes; 66 per cent of men and 72 per cent of women experienced first symptoms before the age of 31 years

Sites involved and sex variations. Hidradenitis affecting axillary and inguinoperineal skin was observed in 83 per cent and 67 per cent of patients respectively; perianal skin involvement was recorded in 12 per cent, mammary skin involvement in 10 per cent. Analysis of the sites involved according to patient's sex revealed similar distributions for axillary (men 83 per cent; women 83 per cent) and inguinoperineal hidradenitis (men 71 per cent; women 66 per cent). In contrast, mammary (anterior chest) disease was more common in women (13 per cent *versus* 2 per cent) and men were more frequently affected by perianal hidradenitis (37 per cent *versus* 3 per cent). Multiple-site disease was observed in 56 per cent of patients, both sexes were affected with similar frequency.

Gynaecological and obstetric histories The mean ± s.d. age at menarche of 87 patients with hidradenitis was 13·5 ± 1·5 years (median 12; range 10–16 years). Four patients reported disease onset at 11, 9, 3 and 1 year before menarche. 'Regular' menstrual cycles were described by 56 (67 per cent) patients, 'irregular' cycles by 25 (30 per cent). Four women had undergone hysterectomy (with ovarian conservation) before onset of hidradenitis. Of those women with 'irregular' periods, 12 (48 per cent) experienced cycles of <15 or >45 days duration. This included a patient with severe oligomenorrhoea and obesity (BMI 47) in whom polycystic ovarian disease and androgen excess had been documented previously.

Regular exacerbations of disease symptoms and signs during the premenstrual phase (the flare) were described by 47 (57 per cent) women. The remainder (40 patients) did not experience any consistent change during their cycle (no flare). 'Regular' menstruation was significantly more frequent in women with premenstrual flare than in those from the no-flare group (χ^2 <0·001; *Table 2*). Active hidradenitis was experienced by 44 (69 per cent) women during one or more pregnancies. A consistent alteration in disease status in pregnancy was described by 20 patients: remission in 14, exacerbation in 6.

Obesity. Mean ± s.d. BMI values for 78 women (28·5 ± 5) and 31 men (27·8 ± 3) with hidradenitis were significantly greater than those of the normal Welsh population derived from data from the Office of Population Census and Surveys men: $n = 217$, mean ± s.d BMI 24·7 ± 3; women: $n = 247$, mean ± s.d. BMI 24·1±4 (P<0·001 unpaired t test for both sexes).

BMI values in the overweight and obese ranges were frequently observed in hidradenitis patients (*Table 3*)

Acne. The prevalence of significant acne in men with hidradenitis was 42 per cent (mean age ± s.d. 34 ± 12 years) and 27 per cent in women (mean age ± s.d. 29·6 ± 10 years)

Hormonal studies

There were no significant differences in the serum levels of 17β-oestradiol, sex-hormone-binding globulin and dehydroepiandrosterone sulphate in patients and controls. Serum levels of testosterone, androstenedione and the androgen index were significantly greater in women from the no-flare group than controls and women with a premenstrual flare (all P < 0·05; Mann–Whitney U test); *Table 4*.

Serum progesterone values were significantly lower in women without premenstrual flare (median 6·3 nmol/l, range <2–29 nmol/l) than in those with a flare (median 25·5 nmol/l; range <2–77 nmol/l; P < 0·05, Mann–Whitney). Subnormal progesterone levels were recorded in nine (50 per cent) women without a flare and in only two women (11 per cent) with

Table 2 *Premenstrual and gynaecological status in 83 women with hidradenitis*

'Flare'	
Regular cycles	41
Irregular cycles	6
Total	47
'No flare'	
Regular cycles	6
Irregular cycles	19
Plus others	
Oral contraceptive users	8
Perimenopausal	2
Peripubertal	1
Total	36

Table 3 *Frequency distribution of 'overweight' and 'obese' body mass index scores in patients with hidradenitis and in population-based controls*

	Hidradenitis	Controls
Men		
n	31	217
Overweight (%)	77*	44
Obese (%)	26*	7
Women		
n	78	247
Overweight (%)	69*	33
Obese (%)	33*	7

*P<0·001, χ^2 test (hidradenitis *versus* controls)

Table 4 *Median (minimum–maximum) values of testosterone, androstenedione and androgen index in women with hidradenitis*

	No flare ($n = 18$)	Flare ($n = 18$)	Controls ($n = 14$)
Testosterone (nmol/l)	1·9 (0·6–4·1)*	1·5 (0·8–3·2)	1·5 (0·7–2·6)
Androstenedione (nmol/l)	6·2 (2·1–13·4)*	4·4 (2·9–8·7)	3·7 (2·9–9·7)
Androgen index	3·5 (0·6–9·7)*	3 (1·7–5·4)	2·4 (1·2–4·4)

* $P < 0·05$; Mann–Whitney *U* test; no flare *versus* flare and no flare *versus* controls

premenstrual exacerbation of disease ($P < 0·05$; Fisher's exact test).

Discussion

In agreement with most previous studies, we have found women to be more frequently affected by hidradenitis than men. The reason for this female preponderance is not clear; paradoxically the relatively high circulating levels of oestrogens and progesterones in women might be expected to exert a protective effect against the onset of an androgen-dependent disorder. Conclusive evidence in support of quantitative differences in apocrine gland mass between men and women is lacking[16,17]. The use of deodorants, talcum powder, antiperspirants or removal of body hair does not account for the female predilection to the disease[18]. This female predisposition to hidradenitis may simply reflect sex differences in the nature of the biochemical lesion causing the disease. Androgen levels in women are normally low and, in contrast to men, even a small increase in circulating levels will provide more substrate for androgen-metabolizing enzymes in target tissues, therefore producing a clinical effect.

Similar profiles in 'age at onset' distribution in men and women suggests common aetiological factors. The frequency distribution curve describing hidradenitis onset in this study is similar and parallels normal variations in the androgen milieu that occur with age. Disease onset in neonates and infants, although uncommon[19], may reflect the relatively hyperandrogenic state evident in the first year of life[20]. In contrast, the few cases of hidradenitis described in children up to the ages of 6–8 years[21,22] may reflect the decline in androgen status which persists until the onset of adrenal androgen synthesis[23]. Peak onset of the disease between 11 and 30 years of age coincides with a marked increase in the androgen milieu after puberty. Histochemical and *in vitro* studies of cutaneous androgen metabolism describe maximal enzyme activity between the ages of 11 and 30 years[24,25]. Morphological studies of apocrine gland secretory activity[16,17] report minimal function in very young children. This increases at the age of 7–8 years and again at puberty. Progressive dilatation of apocrine gland tubules, in addition to the relative decline in androgen status that occurs with increasing age, may explain the reduced propensity to duct occlusion and disease onset after the fifth decade.

The frequency of disease appearing at specific anatomical sites is likely to reflect the absolute number or density of apocrine sweat glands. Apocrine glands are confluent in the axilla, more sparsely distributed in the groin and perineum and least evident in perianal and mammary skin[26,27]. The ratio of men and women affected by axillary or inguinoperineal disease (2:5) is in contrast to that recorded for perianal (5:1) and mammary hidradenitis (1:14). The male predilection to perianal disease may reflect sex differences in the density of perianal and sebaceous apocrine glands[28], although other local factors may also be important in triggering disease at this and mammary sites. There is no evidence for morphological abnormalities of apocrine glands in patients with hidradenitis[26]. Multiple site disease in over 50 per cent of patients suggests a generalized systemic stimulus to disease onset. Although single-site disease was observed in 44 per cent of patients, hidradenitis is often progressive and up to 25 per cent of patients will, in the long term, develop lesions at a previously unaffected site[29].

Menstrual cycle length is highly variable and is affected by both chronological and gynaecological age. Chiazze *et al.*[10] studied 2316 women and found the lowest variations in cycle length between 25 and 39 years. The same authors described 1 per cent of women within this age range as having cycles of duration <20 and >40 days; 15 per cent of women with hidradenitis were outside these limits. Fifty-seven per cent of women reported increased symptoms before the onset of menstruation; Mortimer and co-workers[7] recorded this same phenomenon in 61 per cent of patients, and 70 per cent of women with acne are said to experience similar premenstrual symptoms[30]. We have found an association between premenstrual flare in disease and regular menstruation and, conversely, the absence of flare in association with irregular cycles. The biological basis of an irregular cycle may be an inadequate ovulatory mechanism and there are clinical grounds for suspecting such abnormal cycles in 11 other women from the no-flare group. Oral contraceptive use (eight patients) results in inhibition of ovulation and/or inadequate corpus luteum function[31]. Anovulatory cycles are common in the early years following menarche[32] (one patient) and during the climacteric[33] (two patients).

The exclusion of women with severe acne, hirsutism or menstrual disorder from the hormone study may well explain the failing to demonstrate more pronounced androgen excess in patients with hidradenitis. Nevertheless, the implication that absence of a premenstrual flare reflects anovulatory cycles appears to be substantiated by the findings of low progesterone levels in women from the no-flare group. Furthermore, as an inadequate luteal phase is more likely to reflect than to cause androgen excess[34,35] the relative hyperandrogenaemia of the no-flare group is consistent with abnormal ovarian function and the clinical presentation of these patients.

During pregnancy the clinical course of hidradenitis changed in 45 per cent of patients; similar changes are described in women with acne. The increase in plasma levels of oestrogens, sex-hormone-binding globulin and progesterone will serve to limit androgenic stimulation of apocrine glands; this may account for reduced disease activity described by 60 per cent of this patient group. The mechanism leading to increased disease activity during pregnancy in other women is still not clear.

Altered disease status during the luteal phase and in pregnancy must reflect either direct hormonal effects upon apocrine gland activity and/or an influence upon a tendency to poral occlusion. The latter might include reversible changes in keratin hydration within the apopilosebaceous unit[36] or an alteration in the physicochemical properties of their secretions[37]. Either of these changes could lead to an increase in outflow resistance and predispose to poral block.

Excess body weight in patients with hidradenitis is likely to be a contributory feature in the pathogenesis of the disease. Areas of maximum apocrine gland density are moist, humid and prone to contact with adjacent skin surfaces. This will promote epidermal maceration and follicular plugging with desquamated epithelia and keratin. In addition, obesity even in otherwise healthy men and women is associated with changes in the production, metabolism and biological activity of both androgens and oestrogens[38] and is described as a variable manifestation of mild androgen excess[35]. Obesity may therefore promote the tendency to androgen excess as well as producing a local skin environment that predisposes to disease onset and progression.

The increased prevalence of acne in patients with hidradenitis has been described previously[7]. Sebaceous glands as well as apocrine glands may be involved in hidradenitis[39]. Our findings of acne in 42 per cent of men and 27 per cent of women are consistent with previous reports of this association and confirm the likelihood of a shared pathogenesis with what is recognized as a cutaneous manifestation of androgen excess.

Although many of the clinical features of hidradenitis can be explained by recognized changes in the androgen milieu, the fact remains that hormone levels in most patients fall within the normal range (78 per cent and 89 per cent of patients had normal-range values of testosterone and androdostenedione respectively).

The capacity of apocrine glands to convert inactive androgenic prohormones into biologically active metabolites is likely to play a critical part in the pathogenesis of the disease. Our preliminary studies to assess the end-organ response to androgens *in vitro* indicate that testosterone conversion within subdermal axillary fat laden with apocrine glands is significantly enhanced in women with hidradenitis[40].

References

1. Williams DW. Surgical treatment of hidradenitis suppurativa. *Br J Plast Surg* 1953; **6**: 231–7.
2. Cornbleet T. Pregnancy and apocrine gland diseases: Hidradenitis and Fox–Fordyce disease. *Arch Dermatol Syph* 1952; **65**: 12–19
3. Harrison SH. Axillary hidradenitis. *Br J Plast Surg* 1964; **17**· 95–8.
4. Curtis AC. Cushings syndrome and hidradenitis suppurativa. *Arch Dermatol Syph* 1950; **62**· 329–30.
5. Chalmers RJG, Ea RD, Beck MH, Dewis P, Andersen DC. Acne vulgaris and hidradenitis suppurativa as presenting features of acromegaly *Br J Med* 1983; **287**: 1346–7.
6. Harrison BJ, Kumar S, Read GF *et al*. Hidradenitis suppurativa: evidence for an endocrine abnormality. *Br J Surg* 1985; **72**· 1002–4.
7. Mortimer PS, Dawber RP, Gales MA, Moore RA. Mediation of hidradenitis suppurativa by androgens. *Br Med J* 1985; **292**: 245–8.
8. Sawers RS, Randall VA, Ebling FJG. Control of hidradenitis suppurativa in women using anti androgen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1985; **115**: 269–74
9. Mortimer PS, Dawber RP, Gales MA, Moore RA. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986, **115**. 263–8.
10. Chiazze L, Brayer FT, Macisco JJ, Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. *JAMA* 1968; **203**: 377–80.
11 Knight I. *The Heights and Weights of Adults in Great Britain.* London: HMSO, 1984: 3.
12. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and adults. *Br Med J* 1979; **i**: 1109–10.
13. Dyas J, Read GF, Riad-Fahmy D. A simple robust assay for testosterone in male plasma using an ^{125}I radioligand and a solid phase separation technique. *Ann Clin Biochem* 1979; **16**: 325–31.
14. Smith MR, Rudd BT, Shirley A *et al* A radioimmunoassay for the estimation of serum dehydroepiandrosterone sulphate in normal and pathological sera. *Clin Chim Acta* 1975; **65**. 5–13
15. Rosner W. A simplified method for the quantitative determination of testosterone-estradiol-binding globulin activity in human plasma. *J Clin Endocrinol Metab* 1972; **35**. 983–8.
16. Montagna W. Histology and cytochemistry of human skin *J Invest Dermatol* 1959; **33**: 151–61.
17. Montes LF, Baker BL, Curtis AC. The cytology of the large axillary sweat glands in man. *J Invest Dermatol* 1960, **35**: 273–83.
18. Morgan WP, Leicester G. Depilation and deodorants in hidradenitis suppurativa. *Arch Dermatol* 1982; **118**: 101–2.
19. Ajayi OO, Olurin EO. Hidradenitis suppurativa. *West Afr Med J* 1970; **19**· 173–5.
20. Wilson JD, Walker JD. The conversion of testosterone to 5α-androstan-17β-ol (dihydrotestosterone) by skin slices of man. *J Clin Invest* 1969, **48**: 371–9.
21. Cole HN, Driver JR. Multiple abscesses of axillary sweat glands. *Arch Dermatol Syph* 1929; **19**: 310.
22 Tachau P. Abscesses of the sweat glands in adults *Arch Dermatol Syph* 1939; **40**: 545–50.
23. Cutler GB, Loriaux DL. Adrenarche and its relationship to the onset of puberty. *Fed Proc* 1980, **39**· 2384–90.
24. Calman K, Muir AV, Milne JA, Young H. Survey of the distribution of steroid dehydrogenases in sebaceous glands of human skin. *Br J Dermatol* 1970; **82**: 567–71.
25. Chakraborty J, Thomson J, MacSween MP *et al* The *in-vitro* metabolism of 7-^{3}H dehydroepiandrosterone by human skin. *Br J Dermatol* 1970; **83**: 477–82.
26. Morgan WP, Hughes LE. The distribution, size and density of the apocrine glands in hidradenitis suppurativa. *Br J Surg* 1979; **66**: 853–6.
27 Homma H. On apocrine sweat gland in white and negro men and women. *Bull Johns Hopkins Hosp* 1926; **38**: 365–71
28. Harrison BJ, Castle A, Dawlish F Skin appendages in male and female perianal skin. *Ann R Coll Surg* 1987; **69**: 246.
29. Harrison BJ, Mudge M, Hughes LE. Recurrence after surgical treatment of hidradenitis suppurativa. *Br Med J* 1987, **294**, 487–9.
30. Cunliffe WJ, Cotterill JA The acnes In: Rook A, ed *Major Problems in Dermatology, Vol 6.* London: WB Saunders, 1975· 19.
31. Hawkins DF, Elder MG. *Human Fertility Control. Theory and Practice*. London: Butterworths, 1979: 52.
32. Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. *J Endocrinol* 1983; **97**: 213–19.
33. Doring GK. The incidence of anovular cycles in women. *J Reprod Fertil [Suppl]* 1969; **6**: 77–81.
34. Hosseinian AH, Kim MH, Rosenfield RL. Obesity and oligomenorrhoea are associated with hyperandrogenism independent of hirsutism. *J Clin Endocrinol Metab* 1976; **42**: 765–9
35. Hatch R, Rosenfield RL, Kim MH, Thedway D. Hirsutism implications, etiology and management. *Am J Obstet Gynecol* 1981; **140**. 815–30.
36 Williams M, Cunliffe WJ, Gould D. Effects of hydration on the pilo-sebaceous duct orifice. *Br J Dermatol* 1974; **90**: 631–5
37. Magos A, Studd J. Effect of the menstrual cycle on medical disorders. *Br J Hosp Med* 1985, **33**: 68–77.
38. Kirschner MA, Schneider G, Ertel NH, Worton E. Obesity, androgens, estrogens, and cancer risk *Cancer Res [Suppl]* 1982, **42**: 3281–5.
39. Ebling FJG. Hidradenitis suppurativa: an androgen dependent disorder *Br J Dermatol* 1986; **115**· 259–62
40. Harrison BJ, Hughes LE. Enhanced peripheral androgen metabolism in patients with hidradenitis suppurativa *Br J Surg* 1988; **75** (abstract) 600

Br. J. Surg. 1988, Vol. 75, October,
976–981

Effects of low dose perioperative interferon on the surgically induced suppression of antitumour immune responses

P. C. Sedman,
C. W. Ramsden,
T. G. Brennan,
G. R. Giles and
P. J. Guillou

University Department of Surgery,
St. James's University Hospital,
Leeds, UK
Correspondence to:
Professor P. J. Guillou,
Academic Surgical Unit, Queen
Elizabeth The Queen Mother
Building, St. Mary's Hospital
Medical School, London W2 1NY,
UK

General surgical procedures are followed by a period of generalized immunosuppression that may favour the deposition of metastases seeded at operation in patients with malignant disease. In an attempt to prevent the suppression of host-antitumour immune mechanisms following surgery we have studied the immunological effects of low-dose perioperative interferon-α (r-HuIFNα). Patients were randomly allocated pre-operatively to the control (n = 15) *or treatment group* (n = 15). *Patients in the treatment arm received a 1-week course of subcutaneous recombinant human interferon-α 2a (Roferon-A) at a dose of 2 megaunits daily starting on the evening before surgery. Natural killer cell, lymphokine activated killer cell cytotoxicities and endogenous interleukin 2 production were measured 1 day before surgery and on the first, third, fifth and tenth postoperative days. Treatment with r-HuIFNα did not prevent the postoperative impairment of interleukin 2 production or lymphokine activated killer cell cytotoxicity. However it prevented the fall in natural killer cell activity normally observed following surgery. This may have important consequences in controlling metastatic dissemination of tumour in this vulnerable period.*

Keywords: Gastrointestinal cancer, surgery, immunotherapy, interferon-α

Surgical resection provides the only treatment with realistic curative potential for most solid organ malignancies, including gastrointestinal cancer. However, even after apparently curative primary surgery there remains a depressingly high incidence of tumour recurrence, both at the margins of resection[1] and at distant sites[2]. Such recurrence carries a poor prognosis and may result either from growth of microscopic deposits present at the time of surgery or from the seeding of metastatic cells shed during operative manipulation of the tumour[3,4].

Adjuvant chemotherapy has been advocated by some to prevent this problem but results to date have been disappointing[5,6] and new avenues require exploration. There is now considerable evidence to support the contention that immune defences may influence tumour growth and tumour-directed host responses can readily be demonstrated in humans as well as in experimental animals. Operative procedures are known to result in marked generalized immunosuppression in the immediate postoperative period, not only in patients with benign disease[7,8], but also in patients undergoing cancer surgery[9–11]. This surgically induced immunosuppression in cancer patients may result in accelerated growth of residual tumour[13–18] and provide a fertile soil in which liberated metastases may grow.

Interferons are a group of molecules with stimulatory effects on antitumour immune responses and are now available for clinical use In this prospective randomized clinical trial we have examined the potential role of recombinant human interferon-α (r-HuIFNα) in modifying host antitumour immune responses in the postoperative period in patients with gastrointestinal cancer.

Patients and methods

Patient details

Details of the patients recruited into this study are summarized in *Table 1* All patients were admitted electively for planned resection of pre-operatively confirmed gastric or colorectal tumours. Each gave informed consent to participate in the study which had been granted local ethical committee approval. Upon entry patients were randomly allocated in a blind card fashion into two groups The control group proceeded normally through surgery Patients in the treatment group each received 2 megaunits interferon-α 2a subcutaneously (Roferon-A, Roche Products, Basle, Switzerland) daily for 7 days starting on the evening before surgery. All injections were given at 18.00 h.

Patients were classified as malnourished if there was a history of weight loss of 15 per cent or more in the preceding 6 months and/or a serum albumin concentration <32 g/l and/or a serum transferrin level $<2{\cdot}00$ g/l.

All patients had histologically proven gastrointestinal cancer and disease was regarded as advanced if there was clinical or histopathological evidence of extraserosal tumour spread.

Immunological studies

Baseline immunological studies were performed in each patient one day pre-operatively and repeated on the first, third, fifth and tenth postoperative days. In each instance 30 ml of peripheral venous blood was drawn between 08 00 and 09.00 h and collected in bottles containing 7 drops of preservative-free heparin. Mononuclear cells were isolated on Lymphoprep (Nycomed) density gradients after the method of Boyum[19]. After separation the cells were collected and suspended in complete medium consisting of RPMI 1640 (Gibco Ltd) supplemented

Table 1 *Patient details*

	Controls	r-HuIFNα treatment
n	15	15
Age ± s.d	62 ± 11	74 ± 9
M.F	5:10	7:8
Gastric/colorectal cancer ratio	4:11	2:13
Localized/advanced cancer ratio	4:11	5:10
Malnourished patients	4	4

with 10 per cent Foetal Calf Serum, gentamicin (160 μg/ml), Fungizone (2·5 μg/ml), non-essential amino acids, mercaptoethanol (50 μM) and sodium pyruvate (5 mmol). The cells were counted in a Neubauer counting chamber and diluted in complete medium to the cell density required for each experiment.

Natural killer cell cytotoxicity assay

Natural killer (NK) cell activity was measured using a 4 h chromium release cytotoxicity assay against subclone 6 of the erythroleukaemia cell line K562 as previously described[20]. In brief, 5×10^5 effector cells (freshly isolated mononuclear cells) were incubated with 1×10^4 ^{51}Cr radiolabelled K562 target cells in triplicate wells of round-bottomed microtitre plates (Sterilin Ltd) in a total reaction volume of 200 μl of complete medium. Serial doubling dilutions of effector cells were performed so that effector:target ratios of 50:1 down to 6·25:1 were achieved.

After incubation at 37°C in a humidified atmosphere containing 5 per cent CO_2 for exactly 4 h, 100 μl of supernatant was removed from each well and its radioactivity measured on a Philips Gamma counter. Spontaneous and maximal ^{51}Cr release was measured by incubating 1×10^4 target cells with complete medium alone and with detergent respectively. The percentage specific ^{51}Cr release which represents the percentage lysis of target cells was calculated for each effector:target ratio from the standard formula

(experimental release − spontaneous release)/
(maximal release − spontaneous release) × 100%

Interleukin 2 production

Interleukin 2 (IL-2) production from fresh lymphocytes was stimulated using the standard T cell mitogen concanavalin A (con A) (Sigma Chemicals Ltd). Lymphocytes at a cell concentration of 1×10^6 cells/ml containing 20 μg/ml of con A were divided into two samples. One of these was irradiated with 1200 rad to remove the radiosensitive suppressor cells[21]. For each sample five 200 μl aliquots were added to the wells of flat-bottomed microtitre plates. After 24 h incubation at 37°C in a humidified atmosphere containing 5 per cent CO_2, 100 μl supernatant was removed from each well, pooled into a 500 μl aliquot and stored at −70°C for subsequent batch assay.

Interleukin 2 estimations

IL-2 production was calculated by the ability of the stored con A stimulated lymphocyte supernatants to maintain the proliferation of the IL-2 dependent cell line CTLL-2 according to the method of Gillis[22]. Briefly, serial doubling dilutions of each supernatant were placed in duplicate 100 μl amounts in the flat-bottomed wells of microtitre plates and 100 μl CTLL-2 cells at a cell concentration of 4×10^4 cells/ml were added to each well. The plate was incubated at 37°C in a humidified atmosphere containing 5 per cent CO_2 for 30 h with 1 μCi radioactive [^{3}H]-thymidine being added for the final 6 h. Cells were harvested on a Dynatech 2000 cell harvester and the [^{3}H]-thymidine uptake of cells was measured on a Philips Beta counter. The concentration of IL-2 in each supernatant was then calculated using a log-probit analysis programme and expressed as units per millilitre.

All assays for each patient were performed simultaneously after completion of the study period and in each case an internal IL-2 standard was used to enable subsequent inter patient analysis of results.

Lymphokine activated killer cell generation

For the generation of lymphokine activated killer (LAK) cells, 15×10^6 fresh lymphocytes in 10 ml complete medium containing 1000 units/ml recombinant IL-2 (Roche Products Ltd, Basle, Switzerland) were placed in upstanding tissue culture flasks (Sterilin). These were incubated for 3 days at 37°C in a humidified atmosphere containing 5 per cent CO_2 with gentle agitation twice daily. The cells were then collected, washed once in Hanks' balanced salt solution, resuspended in complete medium and counted for use as effectors in the cytotoxicity assay.

LAK cell cytotoxicity assay

This was performed in the same way as for the NK assay described above. Two NK-resistant target cells were employed; DAUDI is a lymphoblastoid cell line and the international reference target for LAK cell activity and COLO 320 is a cell line derived from a colonic adenocarcinoma.

Effect of peroperative blood transfusion

To examine whether allogenic blood transfusions given peroperatively affect NK activity postoperatively we looked at the degree of NK suppression observed in those patients who had been transfused and those who had not in the two groups. The degree of suppression in each patient was calculated from the formula (NK activity on day 1 − pre-operative NK activity)/(pre-operative NK activity) at the effector:target ratio of 50:1.

Statistical analysis

Statistical analysis was performed between groups using the *t* test for unpaired data and within a group using a paired *t* test. Results are expressed as mean ± s.e.m. and a probability value of $<0{\cdot}05$ was regarded as being statistically significant.

Results

Patient outcome

The details of postoperative outcome in the two groups are summarized in *Table 2*. All patients receiving r-HuIFNα treatment tolerated the injections well. None reported symptoms of myalgia, which is a side-effect frequently noted with higher-dose interferon therapy. The slightly higher mean maximal postoperative temperature in the r-HuIFNα-treated group probably reflects the slightly higher incidence of postoperative chest, urinary or wound infections in this group. There was one postoperative death. This occurred in the control group, 14 days after surgery.

Interleukin-2 production

The results of surgery on maximal interleukin-2 production with and without r-HuIFNα therapy are shown in *Figure 1*. IL-2 production fell dramatically following surgery and this effect was seen maximally on the first postoperative day. There were no significant differences between the interferon-treated and untreated groups at this stage. However, while IL-2 production in the untreated group rose slightly by the third postoperative day this failed to happen in the r-HuIFNα-treated group, in which IL-2 production was significantly lower ($P < 0{\cdot}02$) than that of control patients at this time. By the fifth postoperative day IL-2 production in both groups had returned to levels not statistically different from those seen pre-operatively and this situation persisted until the tenth postoperative day.

Although not shown, the pattern was identical for basal IL-2 production.

Natural killer cell activity

In *Figure 2* the levels of NK cell activity in circulating blood lymphocytes at the effector:target ratio 50:1 are shown pre- and postoperatively in the two groups. NK activity was profoundly suppressed immediately after surgery in the control group ($P<0{\cdot}01$) and remained low until after the fifth postoperative day. Although at day 10 NK cell activity appeared to have risen slightly (P = n.s.) it failed to return to pre-operative values ($P<0{\cdot}05$).

In contrast, NK cell activity in the r-HuIFNα-treated group did not fall significantly in the immediate postoperative period and levels were significantly higher than those seen in the untreated group at postoperative days 1 ($P < 0{\cdot}01$), 3 ($P < 0{\cdot}01$) and 5 ($P < 0{\cdot}05$). In the latter half of the study period, and after cessation of r-HuIFNα therapy there was a trend towards falling NK activity such that by day 10 the levels were significantly lower than those seen pre-operatively in this group ($P < 0{\cdot}05$).

Table 2 *Patient outcome*

	Controls	r-HuIFNα treatment
Peroperatively transfused	9	11
Postoperative status		
Mean max temperature ± s.d. (°C)	37·6 ± 0·5	37·9 ± 0·6
Infections	5	7
Deaths	1	0

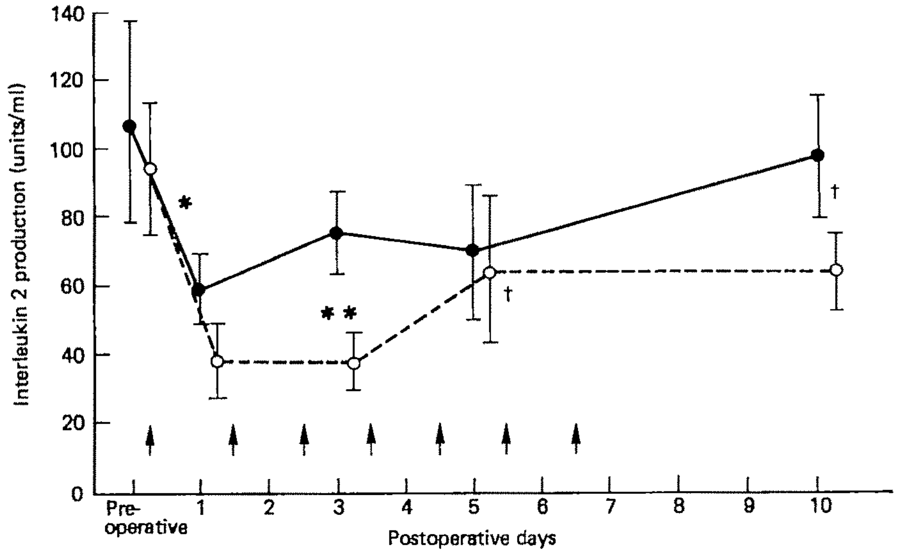


Figure 1 *Maximal interleukin 2 production from con A-stimulated lymphocytes before and after surgery.* ●——● *control group;* ○– – –○ *r-HuIFNα (2 megaunits/day). Pre-operative* versus *postoperative.* *$P<0·05$ *for both groups,* †*n.s. for both groups r-HuIFNα* versus *controls:* **$P<0·02$

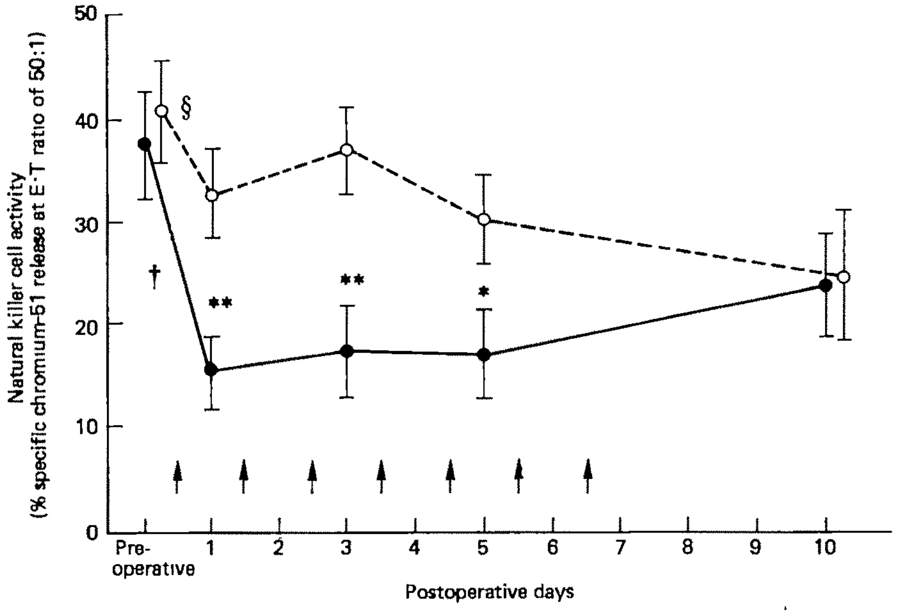


Figure 2 *Natural killer cell activity against K562 levels before and after surgery.* ●——● *control group,* ○– – –○ *r-HuIFNα (2 megaunits/day)* (n = *15 for both groups). r-HuIFNα* versus *controls·* *$P<0·05$, **$P<0·01$. §*Pre-operative* versus *postoperative·* ●, $P<0·01$; ○, *n.s. E.T, effector·target ratio*

LAK cell activity

The changes in LAK cell cytotoxicity after surgery are shown in *Figures 3* and *4*.

Against tumour target DAUDI (*Figure 3*) there was progressive impairment of LAK cell activity postoperatively. However, this did not reach statistical significance until day 3 in the treatment group ($P<0·05$) and day 5 in the control group ($P<0·05$). LAK cell activity remained significantly low on day 10 in both groups. At no time was LAK cell activity significantly different in the r-HuIFNα-treated group compared with controls.

Against tumour target COLO 320 (*Figure 4*) LAK cell activity fell significantly in both groups within 24 h of surgery ($P<0·05$ for controls, $P<0·02$ for r-HuIFNα group). Thereafter LAK cell activity failed to rise significantly again and there was still falling activity at day 10. Again, no significant differences were observed between the control and r-HuIFNα-treated group.

Effect of blood transfusion

Figure 5 shows the effect of blood transfusion on the change in postoperative NK activity. For those patients who received transfusions, a mean of 3·1 ± 1·6 units per patient in the control group and 2·9 ± 1·3 units in the r-HuIFNα-treated group were given (P = n.s.).

No significant changes were seen in either group as a result of transfusion, in the small numbers reported here.

Discussion

Surgical resection remains the treatment of choice for gastrointestinal cancer. However, even after satisfactory macroscopic clearance of tumour, a large proportion of patients succumb to the effects of local recurrence or distant metastases within 5 years of primary surgery[2]. Clearly, this results from residual disease and the logical time to deal with this is at the time of primary surgery. Adjuvant chemotherapy has been disappoint-

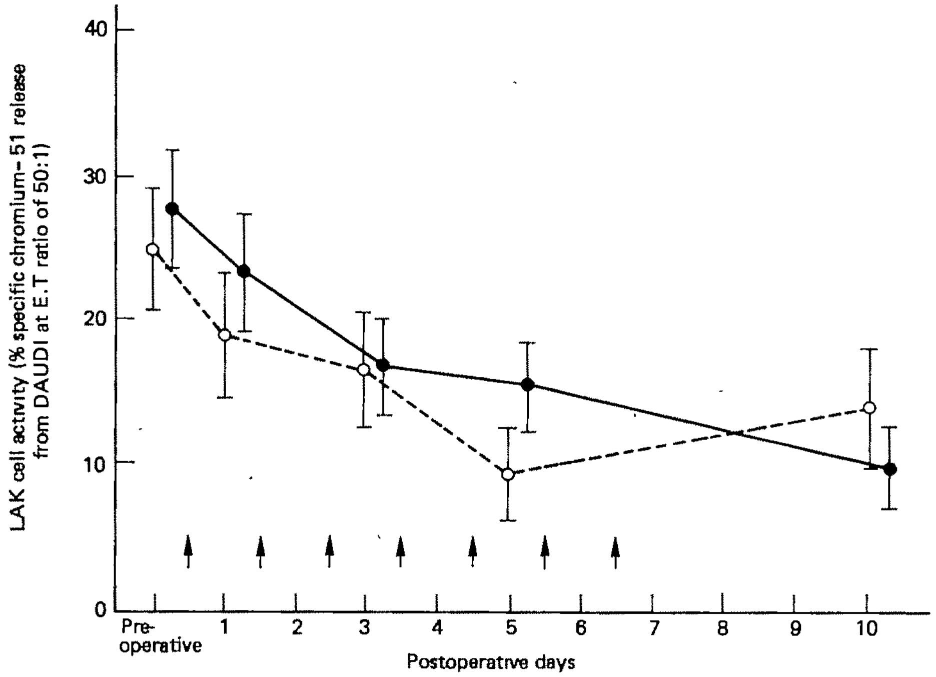


Figure 3 *Lymphokine activated killer (LAK) cell cytotoxicity exhibited against tumour target DAUDI.* ●——● *control group;* ○– – –○ *r-HuIFNα (2 megaunits/day). E·T, effector·target ratio*

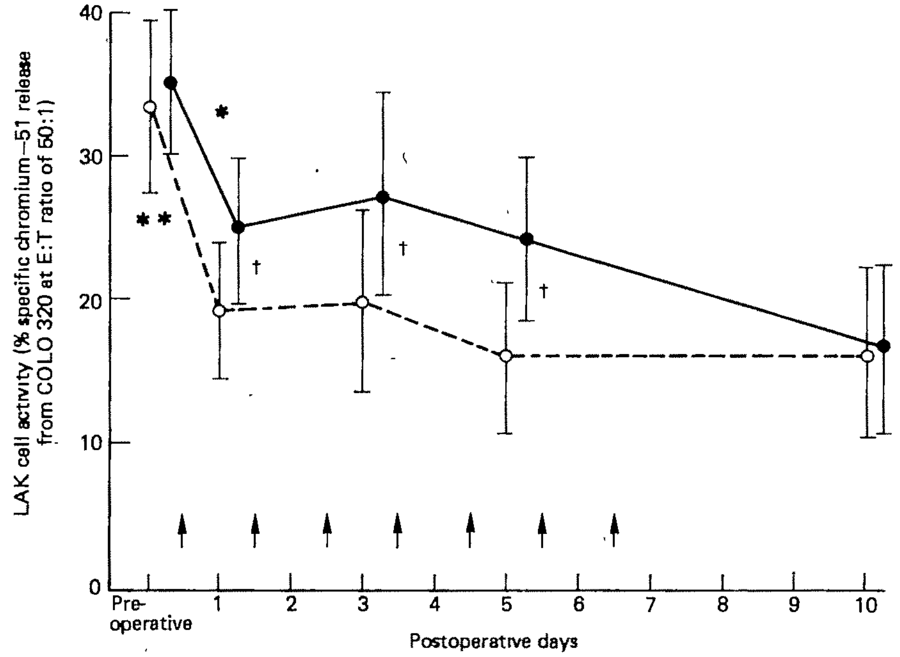


Figure 4 *Lymphokine activated killer (LAK) cell cytotoxicity against an adenocarcinoma cell line COLO 320 pre- and postoperatively in patients with gastrointestinal cancer.* ●——● *control group;* ○– – –○ *r-HuIFNα (2 megaunits/day). Pre-operative* versus *postoperative;* *$P<0\cdot05$, **$P<0\cdot02$, *r-HuIFNα* versus *controls:* †*n.s. E.T, effector target ratio*

ing and an immunological approach deserves consideration in view of recent developments in biotechnology[23]. There is much evidence to suggest that patients undergoing surgical procedures undergo a period of relative immunosuppression immediately postoperatively[7–12]. This depression of immune responses also affects those cellular responses with known anti-tumour efficacy and occurs at the very time when operative manipulation of tumour may liberate tumour cells both locally and systemically[3,24].

In the present study we have examined the immunological effects of a well-characterized, biologically active and clinically available molecule (interferon -α) as an adjunct to surgery for gastrointestinal cancer. This agent was chosen because of its known effects on natural killer (NK) cells[25]. NK cells are a population of lymphocytes widely held to have an immunosurveillance role against metastasizing tumour cells[26]. They are particularly active at the sites of election for metastasis formation[27]. In *Figure 2* it can be seen that, in the control group, NK activity is impaired following surgery, thus confirming the report by Uchida *et al.*[12]. However, this suppression is almost completely prevented by the administration of r-HuIFNα. This effect may have an important bearing on the survival of micrometastatic tumour cells liberated at the time of surgery. Whether the enhanced NK activity seen in this group is due to an increased maturation of cytotoxic cells from inactive precursors, by enhancement of the kinetics of NK cell lysis or by increased recycling of these cells is not clear and may well result from a combination of all three factors. We are therefore

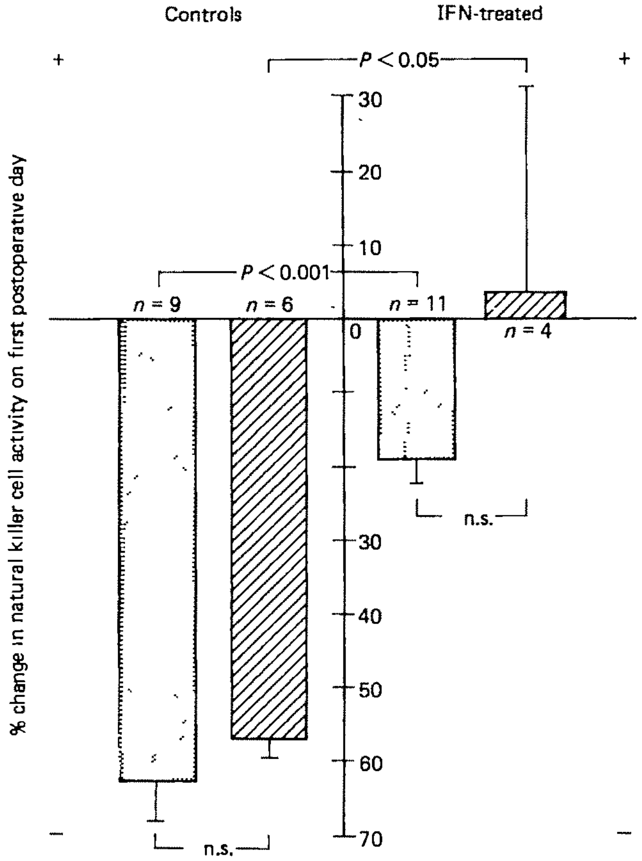


Figure 5 *Effect of peroperative blood transfusion on postoperative change in natural killer cell activity.* ☐ *transfused;* ■ *untransfused*

currently examining lymphocyte phenotype profiles and performing target-binding conjugate assays in an attempt to clarify this mechanism.

In addition to interferons, NK cell activity is also regulated by a number of other cytokines including IL-2[28]. In the presence of sustained high concentrations of this molecule *in vitro*, NK cells develop into lymphokine activated killer (LAK) cells[29]. The characteristics of LAK cell generation in patients with gastrointestinal cancer has already been described elsewhere[30]. LAK cells are potent anti-tumour lymphocytes capable of killing all types of tumour cells *in vitro*, yet remaining non-lytic to normal host cells. When activated *in vitro* and reinfused into tumour-bearing hosts, dramatic clinical remissions have been observed both in experimental animals and in patients with a variety of tumour types[31–33]. Unlike NK cells these lymphocytes exhibit activity against solid tumours.

In *Figures 3* and *4* we show that, in keeping with all other immunological parameters, LAK cell activity is impaired after surgery. This impairment occurs both against tumour target DAUDI (*Figure 3*) and also against the adenocarcinoma COLO 320 cell line (*Figure 4*). It is disappointing that, in contrast to its effect on NK activity, r-HuIFNα failed to augment LAK activity in this study and perhaps other interferon subtypes should be considered[34].

The effects of perioperative r-HuIFNα therapy on the endogenous production of IL-2 is also disappointing IL-2 production is already impaired in patients with gastrointestinal tract cancer[35] and *Figure 1* shows that surgery suppresses it even further. r-HuIFNα does not diminish the degree of suppression and, indeed, may have a detrimental effect.

IL-2 is a molecule of fundamental importance to cellular immune responses. Its presence is required for the clonal proliferation of cytotoxic T lymphocytes as well as having effects on NK cell activity. When IL-2 is absent it has been suggested[36] that immunogenic stimuli may become tolerated rather than elicit the active immune response that would normally occur. As r-HuIFNα therapy fails to augment postoperative IL-2 production a strong argument can be made for combining IL-2 injections with perioperative r-HuIFNα. Such an approach has shown promising results in a murine model[37].

It is now abundantly clear from this and other immunological studies that surgery alone is capable of depressing immune function and this may favour the growth of residual tumour. Allogenic blood transfusions given peroperatively have been claimed by some to be another factor which may favour postoperative tumour recurrence[38], although this is somewhat controversial. If blood transfusions do have an adverse effect the mechanism is most likely to be immunological. With this in mind we have analysed the changes observed in NK activity on the first postoperative day in both the controls and the r-HuIFNα group. Although no statistically significant effect is attributable to blood transfusion in either group (controls or r-HuIFNα), NK suppression was greater in patients who had been transfused. However, patient numbers are small and more studies need to be done before conclusions can be drawn from these data.

In this study we have confirmed that host antitumour immune responses in patients with gastrointestinal cancer are impaired after surgery. However, the suppression of some of these responses may be abrogated by the perioperative administration of immunoactivating agents such as interferons with potentially beneficial effect on postoperative outcome. These findings warrant further investigation of this approach, in combination with other agents such as interleukin 2.

Acknowledgements

We wish to express our thanks to Roche Products for providing us with interleukin-2 and interferon for this study, to Mrs I. Poole for her expert typographical assistance and to Geistlich Sons Ltd, Chester, for their continued support to P. C. Sedman.

References

1. Umpleby HC, Williamson RCN. Anastomotic recurrence in large bowel cancer. *Br J Surg* 1987; **74**. 873–8.
2. Pescatori M, Mattana C, Maria G, Ferrara A, Lucibello L. Outcome of colorectal cancer *Br J Surg* 1987; **74**. 370–2.
3. Salsbury AJ, McKinna JA, Griffiths JD, Naunton Morgan C. Circulating cancer cells during excision of carcinomas of the rectum and colon with high ligation of the inferior mesenteric vein. *Surg Gynecol Obstet* 1965; **120**: 1266–70.
4. Roberts S, Long L, Jonasson O, McGrath R, McGrew E, Cole WH. The isolation of cancer cells from the blood stream during uterine curettage. *Surg Gynecol Obstet* 1960; **111**: 3–11.
5 Bonadonna G, Mathe G, Salmon SE (eds). *Adjuvant Therapies and Markers of Post-Surgical Minimal Residual Disease 2*. Berlin, Heidelberg, New York: Springer-Verlag, 1979.
6. Salmon SE, Jones SE (eds). *Adjuvant Therapy of Cancer*. New York· Grune and Stratton, 1981.
7. Lennard TWJ, Shenton BK, Borzotta A *et al.* The influence of surgical operations on components of the human immune system. *Br J Surg* 1985; **72**: 771–6
8. Slade MS, Simmons RL, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. *Surgery* 1975; **78**: 363–72.
9 Roth JA, Golub SH, Grimm EA, Eilber FR, Morton DL. Effects of operation on immune response in cancer patients: sequential evaluation of *in vitro* lymphocyte function. *Surgery* 1976; **79**: 46–51
10 Kwan Park S, Brody JI, Wallace HA, Blakemore WS. Immunosuppressive effect of surgery. *Lancet* 1971; **i**: 53–5.
11. Cochran AJ, Spilg WGS, Mackie RM, Thomas CE Postoperative depression of tumour-directed cell-mediated immunity in patients with malignant disease. *Br Med J* 1972, **4**: 67–70.
12 Uchida A, Kolb R, Micksche M. Generation of suppressor cells for natural killer cell activity in cancer patients after surgery *J Natl Cancer Inst* 1982; **68**: 735–41.
13 Fielding LP, Wells BW. Survival after primary and staged resection for large bowel obstruction caused by cancer. *Br J Surg* 1974, **61**: 16–18
14. Weese JL, Ottery FD, Emoto SE. Do operations facilitate tumour growth? An experimental model in rats. *Surgery* 1986; **100**: 273–7.

15 Lange PH, Hekmat K, Bosl G, Kennedy BJ, Fraley EE. Accelerated growth of testicular cancer after cytoreductive surgery. *Cancer* 1980, **45** 1498–506.

16. Lundy J, Lovett EJ, Wolinsky SM, Conran P. Immune impairment and metastatic tumour growth. *Cancer* 1979; **43** 945–51.

17. Eggermont AMM, Steller EP, Sugarbaker PH. Laparotomy enhances intraperitoneal tumour growth and abrogates the antitumour effects of interleukin-2 and lymphokine activated killer cells. *Surgery* 1987; **102**. 71–8

18 Saba TM, Antikatzides TG. Decreased resistance to intravenous tumour challenge following surgery. *Br J Cancer* 1976, **34**: 381–9.

19 Boyum A. Separation of leukocytes from blood and bone marrow *Scand J Lab Clin Invest* 1968, **21** (Suppl 97)

20 Guillou PJ, Hegarty J, Ramsden C, Davidson AM, Will EJ, Giles GR. Changes in human natural killer cell activity early and late after renal transplantation using conventional immunosuppression *Transplantation* 1982, **33** 414–21.

21 Chouaib S, Fradelizi D The mechanism of inhibition of human IL-2 production. *J Immunol* 1986, **129**· 2463–8

22. Gillis S, Ferm MM, Ou W, Smith KA T cell growth factor. parameters of production and a quantitative microassay for production. *J Immunol* 1978; **120**· 2027–32.

23. Guillou PJ. Potential impact of immunobiotechnology on cancer therapy *Br J Surg* 1987; **74**· 705–10.

24 Umpleby HC, Fermor B, Symes MO, Williamson RCN. Viability of exfoliated colorectal carcinoma cells. *Br J Surg* 1984; **71**· 659–63.

25. Einhorn S, Herberman RB (eds). *Natural Cell-Mediated Immunity Against Tumors*. New York: Academic Press, 1980. 529–36.

26 Hanna N, Fidler IJ. Role of natural killer cells in the destruction of circulating tumour emboli *J Natl Cancer Inst* 1980; **65**: 801–9.

27. Wiltrout RH, Herberman RB, Zhang SR *et al.* Role of organ-associated NK cells in decreased formation of experimental metastases in lung and liver. *J Immunol* 1985; **134** 4267–75

28. Suzuki R, Handa K, Itoh K, Kumagai K Natural killer cells as a responder to interleukin-2. *J Immunol* 1983; **130**. 981–7.

29 Herberman RB, Hiserodt J, Vujanovic N *et al* Lymphokine activated killer cell activity. Characteristics of effector cells and their progenitors in blood and spleen *Immunol Today* 1987; **8** 178–81.

30. Monson JRT, Ramsden CW, Giles GR, Brennan TG, Guillou PJ. Lymphokine activated killer (LAK) cells in patients with gastrointestinal cancer *Gut* 1987, **28**: 1420–5

31 Lafreniere R, Rosenberg S Successful immunotherapy of murine experimental hepatic metastases with lymphokine activated killer cells and recombinant interleukin-2. *Cancer Res* 1985, **45** 3735–41.

32. Rosenberg SA, Lotze MT, Muul LM *et al* A progress report on the treatment of 157 patients with advanced cancer using lymphokine activated killer cells and interleukin-2 or high dose interleukin-2 alone. *N Engl J Med* 1987, **316** 889–97.

33 West WH, Tauer KW, Yannelli JR. Constant infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. *N Engl J Med* 1987, **316**· 898–905

34 Sedman PC, Ramsden CW, Brennan TG, Giles GR, Guillou PJ Augmentation of lymphokine activated killer cell activity in patients with gastrointestinal cancer *Br J Surg* 1988; **75**· 591–4

35. Monson JRT, Ramsden CW, Guillou PJ. Decreased interleukin-2 production in patients with gastrointestinal cancer. *Br J Surg* 1986, **73**: 483–6

36. Malkovsky M, Medawar PB. Is immunological tolerance (non-responsiveness) a consequence of interleukin-2 deficit during the recognition of antigen? *Immunol Today* 1984; **5** 340–3.

37. Brunda MJ, Bellantoni D, Sulich V *In vivo* anti-tumour activity of combinations of interferon alpha and interleukin-2 in a murine model. Correlation of efficacy with the induction of cytotoxic cells resembling natural killer cells *Int J Cancer* 1987; **40**· 365–71

38. Foster RS, Costanza MC, Foster JC, Wanner MC, Foster CB Adverse relationship between blood transfusions and survival after colectomy for colon cancer *Cancer* 1985, **55** 1195–201.

Br. J. Surg. 1988, Vol. 75, October,
982–983

Cystic change and neoplasia in isolated thyroid swellings

**E. L. Cusick,
C. A. McIntosh,
Z. H. Krukowski and
N. A. Matheson**

*Department of Surgery,
University of Aberdeen, UK
Correspondence to:*
Mr N. A. Matheson, Ward 49,
Aberdeen Royal Infirmary,
Foresterhill, Aberdeen AB9 2ZD, UK

During a 6-year prospective study of clinically isolated thyroid swellings (ITS), 148 (37 per cent) of 395 swellings were cystic as defined by the aspiration of fluid during fine needle aspiration cytology (FNAC). In the 106 (72 per cent) patients operated upon, 47 per cent of the cystic swellings were neoplastic and 14 per cent were malignant. In men 29 per cent of cystic swellings were malignant and 11 per cent in women. Only twelve cystic ITS were permanently abolished by aspiration and FNAC was inaccurate in predicting neoplasia. The incidence of malignancy in cystic ITS is higher than generally accepted and most cysts not abolished by aspiration should be removed.

Keywords: Thyroid cyst, thyroid neoplasia, aspiration cytology

The majority of clinically isolated swellings in the thyroid gland are benign and management is directed to identifying malignant swellings. Malignancy is usually thought to be unlikely in cystic swellings and fluid in a thyroid swelling is therefore often taken to be reassuring[1]. We have found, however, that the physical characteristics of thyroid swellings (as assessed by ultrasound) do not accurately predict pathology[2]. The present prospective 6-year study of the pathology of cystic change in isolated thyroid swellings (ITS) shows that many cystic swellings are neoplastic and an appreciable number are malignant.

Patients and methods

Diagnosis

All patients referred to the thyroid clinic in Aberdeen from September 1981 to August 1987 (6 years) with clinically ITS were submitted to fine needle aspiration cytology (FNAC).

Patients were recorded as having cystic swellings when fluid was aspirated. A swelling was not termed cystic when blood which clotted was aspirated, in distinction to blood-stained fluid which did not clot. Cytological smears, stained with May–Gruenwald–Giemsa and Papanicolaou stains, were made from aspirated material and, when the volume of fluid aspirated was sufficient, from centrifuged samples. Cytological tests were carried out by one cytologist and histological examination of removed swellings by one pathologist with an interest in thyroid pathology. The cytology and histology of every cyst was reviewed at a weekly combined clinico-pathological conference. At these conferences the cytological appearances were classified as benign, suspicious (according to cellularity or nuclear irregularity or crowding), malignant (according to characteristic nuclear features) or unsatisfactory.

Histologically, a cyst with no epithelial cells visible in its lining was classified as of uncertain origin. The presence of a well-defined surrounding fibrous capsule was taken to indicate a neoplastic process. When remaining epithelial elements within the capsule were poorly cellular or consisted largely of colloid lakes the lesion was classified as a colloid adenoma. Classification as follicular adenoma depended on intracapsular cellularity with or without follicle formation. When a follicular neoplasm was diagnosed histologically, 10 blocks (or the whole specimen is less than 10 blocks were possible) were carefully scrutinized for invasive features. Lesions were classified as colloid degeneration, chronic lymphocytic thyroiditis or malignant on conventional criteria.

Patients

During the 6-year period 395 patients with ITS were seen and 148 (37 per cent) were classified as cystic. The details of these patients and their management are shown in *Table 1*. Before August 1982 most patients with ITS underwent operation but thereafter FNAC was used to influence selection of patients for operation[3]. Regardless of the cytology, however, recurrent cyst formation, advanced age, male sex, swelling size and consistency and the patient's wishes were important factors in the decision for or against operation.

Results

Twelve (8 per cent) patients with a cystic lesion abolished by aspiration were discharged without operation. Five patients have been lost to follow-up and twenty-two patients remain under review.

A total of 106 patients with a female:male ratio of 4:1 (85/21) underwent operation. The indications for operation are shown in *Table 1* and the histological results in *Table 2*. In 18

Table 1 *Details of patients and their management*

Total number of patients	395
Solid ITS*	247
Cystic ITS	148
Male	23
Female	125
Reason for operation (106 patients)†	
Malignant/suspicious cytology	36
Recurrent cyst	46
Clinical suspicion	17
Patient request	4
Size/pressure symptoms	11
Policy (before August 1982)	22
No operation	
Discharged	3
Lost to follow-up	5
Continuing follow-up	22
Cyst abolished	12

* ITS, isolated thyroid swelling; † some patients had more than one indication for operation

Table 2 *Histology of 106 resected cystic isolated thyroid swellings*

Histological findings	*n*
Colloid degeneration	18
Colloid adenoma	19
Chronic lymphocytic thyroiditis	1
'Simple' cyst (origin uncertain)	18
Follicular adenoma	35
Malignant	15
Overall	106

Table 3 *Characteristics of fluid aspirated and histological findings in cystic isolated thyroid swellings*

Histology	Volume of fluid aspirated				Colour of fluid aspirated			
	<1 ml	1–5 ml	>5 ml	Not stated	Bloody	Brown	Clear	Not stated
Benign	12	20	24	—	22	17	10	7
Follicular adenoma	9	14	9	3	10	11	7	7
Malignant	3	7	3	2	11	1	—	3
Overall	24	41	36	5	43	29	17	17

(17 per cent) cyst aetiology was obscure because of the absence of lining epithelium. Colloid degeneration accounted for 37 (35 per cent); half of these were encapsulated and therefore termed colloid adenomas although we cannot be certain that such lesions are true neoplasms. The most common cause of thyroid cyst formation however was definite neoplasia in 50 (47 per cent) cases. Follicular adenoma accounted for 35 (33 per cent) and malignant neoplasms for 15 (14 per cent). Of the 15 carcinomas, 7 were follicular, 6 papillary, 1 medullary and 1 anaplastic. Of male patients with cystic ITS, 29 per cent had carcinomas compared with 11 per cent of females but this difference was not statistically significant ($P = 0.09$; Fisher's exact test).

Aspiration cytology was inaccurate in predicting neoplasia in cystic ITS. In the 15 patients with malignant cysts the cytological features were malignant in 4 and suspicious in 6 patients; results of cytological tests were therefore falsely negative in 5 patients In the 55 cysts showing colloid accumulation or an acellular lining, cytology was suspicious (false positive) in 12. There was no relationship between either the volume of fluid aspirated or its colour and the incidence of neoplasia and malignancy (*Table 3*). The differences between the groups were not significant.

Discussion

Since Crile[1] advocated aspiration of thyroid cysts the presence of cystic change in thyroid swellings has been thought to be a reassuring characteristic. There has been a considerable increase in the frequency of diagnosis of cystic change in ITS with the use of both ultrasound and FNAC in pre-operative diagnosis. Ultrasonic scans have shown that 20–44 per cent of thyroid swellings contain fluid[2,4–6] and in the present study fluid was aspirated from 37 per cent of ITS. Ultrasonic scanning has been recommended as a method of selection for operation with conservative management of cystic lesions and removal of solid swellings[7], despite the fact that 27 per cent of cystic swellings removed and 12 per cent of cystic lesions overall were malignant[7].

The aetiology of cystic degeneration in thyroid swellings has not been well described and is, clearly, very varied. An area of colloid degeneration, whether clinically isolated or a generalized abnormality, may contain fluid and degeneration is a common cause of thyroid cyst formation.

'Simple' thyroid cysts with a smooth featureless wall as shown by ultrasound are surprisingly uncommon. In a study of high-resolution ultrasonography in 550 patients only one 'simple' cyst was identified; all the other cystic lesions were either mixed or had some solid material within the lumen or attached to the wall[8]. Cysts with a well-defined capsule probably represent degeneration of a follicular neoplasm[8] and the presence of a rim of surviving adenomatous epithelium is often confirmed if the swelling is removed. Follicular adenoma can be confidently differentiated from follicular carcinoma only by obsessive histological searching for capsular invasion or angioinvasion and there is no reason why this should not also apply to lesions which have undergone spontaneous central necrosis.

Cystic change in papillary carcinoma is well described and we have seen anaplastic cancer present as an ITS with cystic change; despite early operation and resection the clinical course was rapidly fatal.

The frequency of neoplasia and malignancy in this series is little different from that in solid lesions. It contrasts with the very low frequency of detection of malignancy of 2 per cent reported in 200 ITS in whom ultrasonic scanning was used to select patients for operation[6] Crile[1] stated that less than 2 per cent of thyroid carcinomas contain fluid but during this 6-year study 23 per cent of all thyroid carcinomas were cystic.

The more frequent diagnosis of cystic change in ITS by ultrasound or FNAC is a function of increasing accuracy in defining the physical nature of thyroid swellings. The demonstration of fluid, however, is of limited value in predicting underlying pathology and unless a swelling yields clear fluid, or is permanently abolished by aspiration, suspicion of neoplasia should be no less than in apparently solid lesions. Even those which satisfy these criteria are often probably degenerate follicular neoplasms and 'a lingering doubt... that they are necessarily benign'[9] is inevitable.

Unfortunately, we have not found FNAC to be accurate in predicting neoplasia or malignancy in cystic ITS. Many cysts yield relatively acellular fluid showing only a few follicular cells and typically macrophages. Of 15 malignant thyroid cysts, 5 were cytologically falsely negative; this serious inaccuracy is no doubt attributable to difficulty in sampling what may be a relatively small localized or thinly dispersed cellular component. We therefore think at present that most cysts which are not abolished by one or two aspirations should be removed However, the risk of malignancy, as in solid swellings, appears to be lower in women than in men and may be lower when the aspirate is clear rather than blood stained.

Acknowledgements

The cytological tests were performed by Dr V. M M. Williams and the histological examinations by Dr S. W B Ewen.

References

1 Crile G. Treatment of thyroid cysts by aspiration *Surgery* 1966; **59**: 210–12

2. Al-Sayer HM, Bayliss AP, Krukowski ZH, Matheson NA. The limitations of ultrasound in thyroid swellings. *J R Coll Surg Edinb* 1986; **31**: 27–31.

3. Al-Sayer HM, Krukowski ZH, Williams VMM, Matheson NA Fine needle aspiration cytology in isolated thyroid swellings. a prospective two year evaluation. *Br Med J* 1985, **290**: 1490–2.

4. Rasmussen SN, Christiansen NJB, Jorgensen JS, Holm HH Differentiation between cystic and solid thyroid nodules by ultrasonic examination *Acta Chir Scand* 1971; **137**: 331–3

5. Thijs LG. Diagnostic ultrasound in clinical thyroid investigation. *J Clin Endocrinol Metab* 1971; **32**. 709–16.

6 Walker J, Findlay D, Amar SS, Small PG, Wastie ML, Pegg CAS. A prospective study of thyroid ultrasound scan in the clinically solitary thyroid nodule *Br J Radiol* 1985; **58**: 617–19

7. Rosen IB, Walfish PG, Miskin M. The application of ultrasound to the study of thyroid enlargement. *Arch Surg* 1975, **110**. 940–4.

8. Simeone JF, Daniels GH, Mueller PR *et al* High resolution real time sonography of the thyroid *Radiology* 1982; **145**: 431–5.

9. Miller JM, Hamburger JI, Taylor CI Is needle aspiration of the cystic thyroid nodule effective and safe treatment? In: Hamburger JI, Miller JM, eds. *Controversies in Clinical Thyroidology*. New York: Springer-Verlag, 1981 208–17

Br. J. Surg. 1988, Vol. 75, October,
984–987

Renal transplantation in patients over 55 years old

G. Lauffer,
J. A. Murie, D. Gray,
A. Ting and
P. J. Morris

Nuffield Department of Surgery (Transplant Unit), University of Oxford, Churchill Hospital, Oxford, UK

Correspondence to:
Mr J. A. Murie, Nuffield
Department of Surgery, John
Radcliffe Hospital, Oxford
OX9 9DU, UK

From 1975 to 1987, 507 patients, of whom 63 (12·4 per cent) were over 55 years old at the time of operation, received first cadaver renal transplants. The annual percentage of recipients given transplants after the age of 55 has risen from 0 per cent in 1975 to 44 per cent in 1987. Of the 63 older patients, 41 had at least one serious non-renal disease at the time of transplantation. Perioperative mortality rate was 3 per cent. After successful transplantation these patients remained subject to a significant number of serious complications, even in the cyclosporin era. Despite these adverse factors, actuarial graft survival for the population over 55 years of age was no worse than for those patients receiving first cadaver grafts who were under 55 years old, although patient survival was poorer in the former group ($P = 0{\cdot}027$). Analysis of the subgroup of 56 patients treated with an immunosuppression protocol containing cyclosporin failed to show any adverse effect of age on either graft or patient survival. It is concluded that renal transplantation can be as successful in patients over 55 years of age as it is in younger patients and, given an adequate supply of kidneys, should be considered the treatment of choice for the elderly patient with end-stage renal failure.

Keywords: Renal transplantation, cyclosporin

Provisional figures for 1986 (the last year available) from the Registry of the European Dialysis and Transplant Association suggest that 2647 new patients were accepted for treatment of end-stage renal failure in the UK in that year. Forty-seven per cent of these patients were over 55 years of age. For the older population with renal failure, management is generally by hospital dialysis, which is a particularly expensive treatment option[1]. Although transplantation might be considered attractive for this population, relatively few older patients receive transplants as the results have previously seemed too poor to justify the use of scarce resources. Concern that immunosuppression may be poorly tolerated by the older patient after transplantation and that the risk of a variety of complications due to concurrent disease may be excessive is understandable, but hard evidence for such concern is scarce in the modern era of transplantation.

Because of the superior quality of life offered and the relatively low cost, renal transplantation must be the preferred mode of treatment for end-stage renal failure at all ages, if it can be done successfully. The success of transplantation in the young is beyond doubt. With improved immunosuppression using cyclosporin, transplantation is now being offered to increasing numbers of older patients. In this paper we describe the problems encountered in transplanting patients over 55 years of age and present an analysis of outcome for these patients. This outcome is compared with that achieved in younger age groups treated with different immunosuppressive protocols.

Patients and methods

The prospective records of all renal transplant recipients from the inception of the Transplant Service in January 1975 to December 1987 were reviewed to identify those who were 55 years of age or older at the time of transplantation. Sixty-seven patients were identified and all had received transplants from cadaveric donors Of 63 patients who were recipients of first cadaver grafts, 56 had received cyclosporin in their immunosuppression protocol. Disease, apart from that responsible for the renal failure, was common in these patients and was analysed together with surgical outcome and postoperative problems.

Dialysis in Oxford is offered to any patient who would benefit from the treatment, without any defined limit of age, and it has been our policy to accept for transplantation anyone who might benefit from such treatment and for whom the risks of anaesthesia, surgery and immunosuppression are not unduly great. These risks have, of course, changed over the time period of this study.

Before 1978, HLA-A and HLA-B matching was used for renal transplant recipient selection and the best possible match was generally sought[2] Starting in 1978, recipient selection was based on HLA-DR matching, with a similar selection policy operating for all age groups[3]. Pretreatment of non-transfused recipients with three random blood transfusions was introduced in 1983 and, again, a similar policy operated for all age groups[4]. A variety of immunosuppression protocols has been used over the period of the study. Azathioprine and prednisolone were used from the inception of the transplant service in 1975 to 1980, although a marked reduction in steroid dose was introduced in 1978[5] From 1980, the majority of patients have received cyclosporin, either alone with conversion at 3 months after transplantation to azathioprine and prednisolone, or combined with these two drugs as triple therapy from the time of transplantation The exact details of the immunosuppression protocols have been described elsewhere[6–9] but as the majority of older patients received cyclosporin, particular attention has been paid to this subgroup in the present analysis. Renal allograft and patient survival for the over-55-year-old age group and for the larger cohort less than 55 years of age was expressed actuarially[10].

Results

From January 1975 to December 1987, 507 patients received first cadaver renal transplants; 63 (12·4 per cent) of these patients were over 55 years of age at the time of operation. The proportion of over-55-year-olds has increased over this time period from zero in the early years to 44 per cent in 1987 (*Figure 1*). The mean age of this older population of allograft recipients was 60 ± 3 (s.d.) years and the oldest patient to receive a kidney was 67 years. The pathological conditions responsible for renal failure in the older age group were similar to those in younger patients, although both hypertensive nephropathy and polycystic kidney disease were commoner in those over 55 (*Table 1*).

Serious non-renal disease was common in those over 55 years of age, with only 22 (35 per cent) patients being free of

0007–1323/88/100984–04$3 00

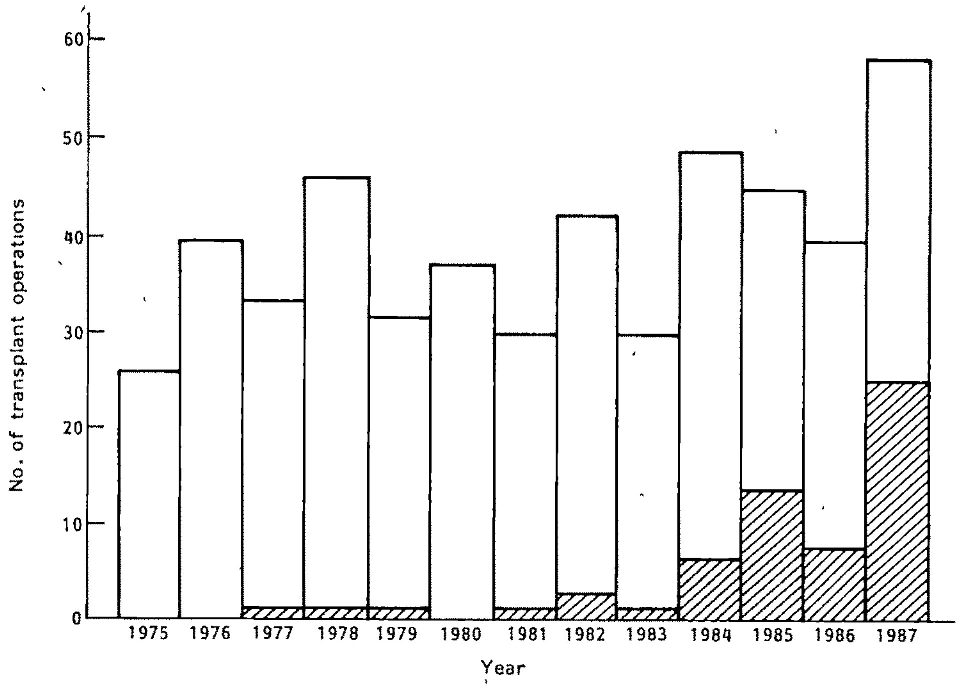


Figure 1 *Number of first cadaver renal transplants performed annually from 1975 to 1987, showing numbers of patients <55 years of age (□) and >55 years of age (■) at the time of operation*

Table 1 *Pathological conditions causing end-stage renal failure in recipients of first cadaver grafts over the age of 55 years*

Pathological condition	*n* (%)
Chronic glomerulonephritis	19 (30)
Hypertension	13 (21)
Polycystic kidney disease	11 (18)
Chronic pyelonephritis	6 (10)
Calculous disease	3 (5)
Diabetes	3 (5)
Gout	1 (2)
Rheumatoid arthritis	1 (2)
Unknown	6 (10)
Total	63

concurrent major disease at the time of transplantation. The remaining 41 patients had 54 separate recognizable pathological conditions (and 9 of the 41 had more than one) of which cardiovascular disease (previous myocardial infarction, angina or previous coronary artery surgery) was commonest, followed closely by moderate to severe respiratory disease (*Table 2*). The influence of concurrent chest or cardiovascular disease on the difficulty of anaesthesia was not easy to assess. While there did not, in general, appear to be any unexpected anaesthetic problems during surgery, it is worthy of note that two patients over 55 years of age had cardiopulmonary arrests shortly after the transplant procedure. One made a full recovery whereas the other died 44 days after operation, a period during which he failed to regain consciousness. A second death occurred from a ruptured abdominal aortic aneurysm on the first postoperative day, giving a perioperative mortality rate of 2 (3 per cent) out of 63 patients.

The only significant technical surgical problem related to age was difficulty with the arterial anastomosis. Sixty-one grafts were anastomosed end-to-side with an aortic patch to the external iliac artery and two end-to-end to the internal iliac artery. Atheroma caused some degree of technical difficulty in 14 (22 per cent) patients and in one case thrombosis in a proximal iliac artery aneurysm, probably caused by the application of vascular clamps, was almost certainly the cause of graft failure.

Table 2 *Serious non-renal pathological conditions identified before transplantation in 41 of 63 transplant recipients over 55 years of age*

Pathological condition	*n* (%)
Cardiovascular disease	14 (26)
Respiratory disease	13 (24)
Peripheral vascular disease	6 (11)
Diabetes	5 (9)
Hyperparathyroidism	4 (7)
Valvular cardiac disease	2 (4)
Hypothyroidism	2 (4)
Osteoporosis	2 (4)
Neurogenic bladder	1 (2)
Guillain–Barré syndrome	1 (2)
Gastric ulcer	1 (2)
Tuberculosis	1 (2)
Legionnaire's disease	1 (2)
Depression	1 (2)
Total	54

After transplantation the surviving older patients continued to be subject to a large number of complications, even in the cyclosporin era. In the first month after transplantation 8 per cent of patients had cardiorespiratory complications and 11 per cent had infections requiring treatment. After the first month, 15 per cent had cardiorespiratory complications, 23 per cent had infections and 25 per cent had steroid-related problems.

A comparison between younger and older age groups of transplant recipients with respect to graft rejection is made difficult because of a variety of extraneous factors, most notably the changes in the immunosuppressive protocols over the years. If the total population over 55 years old is compared simply with the total younger population, no difference in actuarial graft survival can be demonstrated (*Figure 2* and *Table 3*) although patient survival is poorer in the older age group ($P = 0{\cdot}027$) (*Figure 3* and *Table 3*). As 56 (89 per cent) of the 63 over-55-year-olds were treated using a protocol containing cyclosporin[6–9], this group was compared with the analogous cyclosporin-treated subgroup of younger patients. Again, no statistical difference in actuarial graft survival was found, nor, for these subgroups, was there any difference in patient survival

(*Table 4*). The smaller subgroups of those receiving triple therapy with azathioprine, prednisolone and cyclosporin[8], our current immunosuppressive regimen, were also examined. Forty-four patients over 55 years of age had received triple therapy and their actuarial graft survival did not differ significantly from that for the comparable younger group; patient survival for the older group was, however, poorer ($P = 0{\cdot}019$).

Over the period of study (January 1975 to December 1987) 19 out of the 63 older patients lost their transplants and in 7 (37 per cent) instances this was due to death of recipients with functioning grafts (*Table 5*). Of the 246 transplants lost in the younger age group, 72 (29 per cent) were because of death of recipients with functioning grafts. These figures do not reach statistical significance.

Discussion

Advanced age is often assumed to be a contra-indication to renal transplantation on the grounds that older patients may respond badly to immunosuppression, may be at risk from anaesthesia and surgery and may be particularly prone to post-transplant complications. Before the early years of this decade there was good reason for such a negative attitude. In 1978 the Registry of the European Dialysis and Transplantation Association reported an adverse influence of age on the outcome of cadaveric transplantation and in 1977 the Minneapolis group reported a higher mortality with cadaveric renal transplantation than with chronic dialysis in those over 45 years old[11]. Even by 1981 the picture had changed little, for although living-related transplantation in older patients had some advocates, graft survival in patients over 50 years old receiving cadaver kidneys was only 43 per cent and 32 per cent at 2 and 4 years post-transplant respectively[12].

From about 1981 onwards, however, there have been several reports of acceptable results for cadaver renal transplantation in older patients. At 1 year post-transplant, patient survival rates of 73–88 per cent and graft survival of 66–75 per cent have been reported in over-55-year-olds[12–15] with comparable rates of 83 per cent for patient survival and 61 per cent for graft survival in over-50-year-olds[16]. Although these studies have all involved rather small numbers of patients with a limited follow-up, their results are compatible with the present larger study in which patient survival at 1 year was 87 per cent and graft survival 73 per cent. The present study also indicates that it is not only possible to achieve good results with cadaver renal transplantation in the short term (up to 1 year) but also that these results are unlikely to change dramatically in the medium term (2–5 years).

Eighty-nine per cent of transplant recipients in the present series were immunosuppressed using a protocol containing cyclosporin. Unfortunately, the numbers treated without this drug were too small to allow a useful comparison, but it does seem likely that cyclosporin has been beneficial in terms of graft survival and, possibly, also in terms of patient survival. In the USA cyclosporin was introduced at the end of 1983 with a subsequent improvement in 1-year cadaver graft survival rate, from 62 per cent in 1983 to 68 per cent in 1984[17]. Other studies have also demonstrated improved survival rates for grafts with cyclosporin[18]. While a cyclosporin effect in the present study may in part explain similar graft survival in the older age group (most of whom received cyclosporin) when compared with the

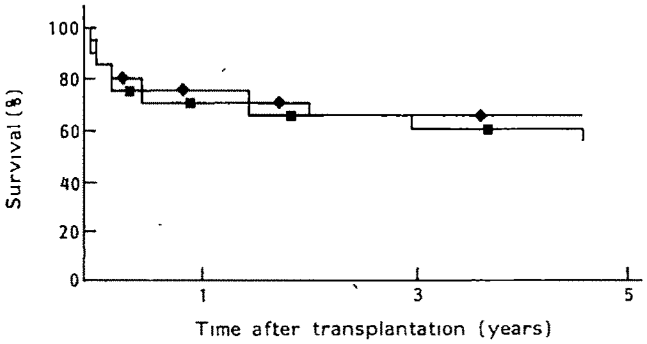


Figure 2 *Actuarial graft survival for 5 years in 444 under-55-year-old (■) and 63 over-55-year-old (◆) first cadaver renal transplant recipients*

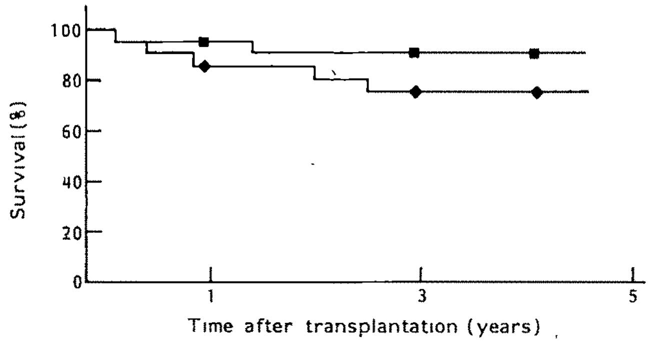


Figure 3 *Actuarial patient survival for 5 years in 444 under-55-year-old (■) and 63 over-55-year-old (◆) first cadaver renal transplant recipients*

Table 3 *Graft and patient survival in first cadaver renal transplant recipients*

Age (years)	No. of transplants	Percentage graft survival (time after transplantation in years)			Percentage patient survival (time after transplantation in years)		
		(1)	(3)	(5)	(1)	(3)	(5)
<55	444	69	62	56	94	91	86
≥55	63	73	63	63	87	76	76

Table 4 *Graft and patient survival in first cadaver renal transplant recipients receiving cyclosporin*

Age (years)	No. of transplants	Percentage graft survival (time after transplantation in years)			Percentage patient survival (time after transplantation in years)		
		(1)	(3)	(5)	(1)	(3)	(5)
<55	172	74	67	64	93	91	87
≥55	56	77	73	73	88	82	82

Table 5 *Cause and time of death after transplantation in patients dying with functioning and non-functioning allografts*

Cause of death	Transplant functioning at death	Time after transplantation (days)
Septicaemia	Yes	579
Myocardial infarction	Yes	521
Pneumonia	Yes	273
Myocardial infarction	Yes	230
Hypoglycaemia (?insulin overdose)	Yes	115
Cardiorespiratory arrest*	Yes	44
Ruptured aortic aneurysm*	Yes	1
Myocardial infarction	No	1211
Septicaemia	No	70
Tuberculosis/pancreatitis	No	60
Myocardial infarction	No	54
Pulmonary embolism	No	52
Myocardial infarction	No	—

* Perioperative death

total younger age group, it cannot explain similar graft survivals in the older and younger age groups which were both managed using cyclosporin. As death with a functioning graft was commoner in older patients, it may be that some compensating mechanism was at work in this group. A reduced ability in the older patient to mount an immune response against an allograft has been suggested[15].

Overall patient survival, unlike graft survival, was poorer for older patients, although when those over 55 years managed with cyclosporin were compared with those less than 55 years managed similarly, no statistical difference in patient survival could be shown. In this study 37 per cent of graft losses in the over-55-year-olds were owing to deaths of recipients with functioning grafts, compared with 29 per cent for those younger than 55 years old. Although these figures are not statistically different, this is probably attributable to a combination of relatively small numbers and limited follow-up as it is inconceivable that older patients do not die with greater frequency than younger patients. While this point is of some interest, it is perhaps more relevant to consider whether or not transplantation provides better care than dialysis for over-55-year-olds. This study has shown that cadaveric renal transplantation in the older age group provides excellent results which rival those obtained in younger patients, for whom transplantation is now universally considered as the treatment of choice.

It should, nevertheless, be appreciated that although graft survival in the older age group was similar to that for younger patients, the patients themselves were rather different. Of recipients over 55 years of age, 65 per cent had a concurrent major disease at the time of transplantation and 16 per cent had more than one concurrent disease. Careful selection of patients and attention to co-existing diseases before transplantation is required if good results are to be obtained. Technical problems may arise because of atheroma in the iliac vessels[19] and the surgeon must be prepared to undertake difficult arterial anastomoses. In the present study an iliac artery aneurysm caused the loss of one allograft and a ruptured abdominal aortic aneurysm caused the early death of a patient. Occlusive disease may be adequately detected before operation simply by palpation of the femoral pulses, but the problem of aneurysm may be better assessed by ultrasonography of the aorto-iliac segment.

In the post-transplant period, while cardiorespiratory disease continued to cause morbidity, infective and steroid-related complications were also frequently encountered. It may be that steroid should be used particularly sparingly in the older age group and even cyclosporin has been advocated in less than standard doses[14]. Despite these difficulties, the results obtained demonstrate that cadaveric renal transplantation can be very successful in over-55-year-olds. Mortality is no higher than on dialysis and quality of life is improved. From a strictly medical stance, it is no longer justifiable to set arbitrary age limits for potential recipients of renal transplants. Indeed, renal transplantation must be considered now the treatment of choice for the elderly patient with end-stage renal failure, just as it is in the younger patient, not only because of the better quality of life with transplantation, but also on strong economic grounds.

If age is not to limit transplantation and if resources can be made available, are there enough suitable kidneys? It is estimated that abandoning a 55-year-old age limit for renal transplantation could result in a 50 per cent increase in the number of renal transplant operations required. With such an open policy, the Stockholm group require 40 transplants per million population per year[15]. In Stockholm, as in Oslo and Berlin, it has become possible to retrieve 40–50 cadaver kidneys per million population per year and in Innsbruck 80 cadaver kidneys per million population are harvested annually. In contrast, in the UK only 13 kidneys per million per year are obtained, which is far from adequate if we are to offer the best treatment possible to our uraemic population.

References

1. Thompson JF, Chapman JR Dialysis and transplantation In. Morris PJ, ed. *Kidney Transplantation—Principles and Practice*, 2nd edn London: Grune and Stratton, 1984. 33–58.
2. Morris PJ, Oliver D, Bishop M *et al.* Renal transplantation. A new unit's experience. *Lancet* 1978; **ii**: 1353–6.
3. Ting A, Morris PJ. A powerful effect of HLA-DR matching on survival of cadaveric renal allografts. *Lancet* 1980; **ii** 282–5.
4. Opelz G. Blood transfusion and renal transplantation. In· Morris PJ, ed *Kidney Transplantation—Principles and Practice*, 2nd ed. London. Grune and Stratton, 1984: 323–34.
5. Morris PJ, Chan L, Ting A. Low dose oral prednisolone in renal transplantation. *Lancet* 1982; **i**: 525–7.
6. Jaskowski A, Jones RM, Murie JA, Morris PJ. Urological complications in 600 consecutive renal transplants. *Br J Surg* 1987, **74**: 922–5
7. Morris PJ, French ME, Dunnill MS *et al* A controlled trial of cyclosporin in renal transplantation with conversion to azathioprine and prednisolone after three months. *Transplantation* 1983, **36**: 273–7.
8. Jones RM, Murie JA, Allen RD, Ting A, Morris PJ Triple therapy in cadaver renal transplantation *Br J Surg* 1988, **75**: 4–8.
9. Morris PJ, Chapman JR, Allen RD *et al.* Cyclosporin conversion versus conventional immunosuppression· long-term follow-up and histological evaluation. *Lancet* 1987, **i**: 586–91
10. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977; **35**. 1–39.
11. Najarian JS, Kjellstrand CM, Simmons RL. High risk patients in renal transplantation *Transplant Proc* 1977; **9**: 111–15.
12. Sommer BG, Ferguson RM, Davin TD *et al* Renal transplantation in patients over 50 years of age *Transplant Proc* 1981; **13** 33–5.
13. Von Thiel G, Sieber C, Uebersax S, Tondelli P, Harder F, Brunner FP. Leichennierentransplantation bei Patienten uber 55 Jahren *Z Urol Nephrol* 1981; **74**. 821–5.
14. Taube DH, Winder EA, Ogg CS *et al.* Successful treatment of middle aged and elderly patients with end stage renal disease *Br Med J* 1983; **286**· 2018–20.
15. Ost L, Lundgren G, Groth CG. Renal transplantation in the older patient. In: Morris PJ, Tilney NL, eds. *Progress in Transplantation, Volume 2*. London. Churchill Livingstone, 1985. 1–15
16. Okiye SE, Engen DE, Sterioff S *et al.* Primary renal transplantation in patients 50 years of age and older. *Transplant Proc* 1983, **15**: 1046–9.
17. Eggers PW Effect of transplantation on the Medicare End-stage Renal Disease Program. *N Engl J Med* 1988, **318**· 223–9.
18. The Canadian Multicentre Transplant Study Group A randomized clinical trial of cyclosporin in cadaveric renal transplantation: analysis at three years. *N Engl J Med* 1986, **314**: 1219–25.
19. Geis WP, Giacchino JL, Jacobi RJ, Vaz AL. Technical considerations in elderly renal allograft recipients *Am J Surg* 1976; **132**: 332–5.

Br. J. Surg. 1988, Vol. 75, October,
988–992

Testicular torsion in Bristol: a 25-year review

J. B. Anderson and
R. C. N. Williamson

University Department of Surgery,
Bristol Royal Infirmary, Bristol, UK
Correspondence to.
Professor R. C. N. Williamson,
Department of Surgery, Royal
Postgraduate Medical School,
Hammersmith Hospital, Du Cane
Road, London W12 0HS, UK

To identify changes in incidence, presentation, management and outcome, 670 patients with torsion of the spermatic cord presenting in Bristol between 1960 and 1984 have been reviewed. Among the susceptible population of 150 000, the annual incidence of torsion has increased fourfold from 11·2 cases between 1960 and 1964 to 42·8 cases between 1980 and 1984. Throughout this period >90 *per cent of patients have been managed by general surgeons. Patients aged between 12–18 years comprised 62 per cent but 20 per cent were 21 years or older. Torsion was commoner in the cold months, 24 per cent of cases occurring during December and January* ($\chi^2 = 30{\cdot}26$, $P < 0{\cdot}01$)*. When acute torsion was relieved within 12 h of the onset of symptoms only 4 per cent of affected testes were considered non-viable, but beyond this time 75 per cent of patients received orchidectomy. Overall, 238 of 624 (38 per cent) acutely twisted testes were found to be infarcted at operation, and a further 35 patients (6 per cent) had marked testicular atrophy on review 3 months later. The testicular salvage rate has steadily improved from 45 per cent in the years 1960–64 to 67 per cent in 1980–84. Much of the increased incidence of testicular torsion is likely to reflect a greater awareness of the condition by general practitioners. It has been more than matched by an improvement in testicular salvage rate because of earlier referral.*

Keywords: Spermatic cord torsion

Hutchinson, in 1895, wrote[1] 'The forms of acute inflammation of the testis which lead to atrophy are, I believe, usually in some sense neurotic in origin'. Since that time acute scrotal pathology has transferred from the province of the psychiatrist to that of the surgeon. Early reports that testicular torsion was uncommon[2,3] were countered by our previous findings in Bristol that there is an annual incidence of one case per 4000 males below the age of 25[4]. In support, epidemiological data show a rise in the hospital discharge rates for torsion of the testis from 10·7 per 100 000 in 1968 to 27·0 per 100 000 in 1980[5]. Torsion of the spermatic cord is thus a common condition requiring prompt recognition and operation to preserve a viable gonad.

Until the last 25 years the results of urgent surgical intervention for torsion were dismal, with loss of up to 90 per cent of testes[3]. These results could obviously be improved by earlier diagnosis and referral. Operation within 5 h of the onset of symptoms gave an 83 per cent testicular salvage rate in one series, compared with 20 per cent if more than 10 h had elapsed[6]. There has been a steady improvement in the overall rates for testicular salvage, with recent figures ranging from 75 to 79 per cent[7–9]. Even better figures may be obtained through an aggressive policy of exploring every young patient without clear-cut evidence of infection, although epididymitis may then be encountered more often than torsion[10,11].

The continuing difficulty in the diagnosis of testicular torsion has prompted the present review of what is now one of the commonest surgical emergencies in young males. We have studied retrospectively 670 patients with proven torsion of the spermatic cord treated in Bristol between 1960 and 1984 seeking in particular changes in incidence, treatment and outcome during this 25-year period.

Patients and methods

The study is based on 670 cases of testicular torsion admitted during the 25-year period 1960–84 to all hospitals in the Bristol area with acute surgical beds. Patients treated between 1960 and 1974 ($n = 293$), who represent less than half the total case material, formed the basis of a previous report[4]. They are included in the overall review, though extra data were available for the 377 patients seen between 1975 and 1984.

A retrospective review of the operation register kept in each operating theatre throughout Bristol provided the name and hospital record number of every patient undergoing emergency scrotal surgery. The relevant case notes were then obtained, and all who had experienced torsion of the testis, confirmed at operation, were included. Neonatal cases of extravaginal testicular torsion were excluded from this study. In addition, a search of the records of the Hospital Activities Analysis (HAA) Department provided a complete record of all patients with a final diagnosis of testicular torsion based on the discharge summary. Within this group were those who had probably undergone torsion but had not come to operation, either because they did not seek medical attention in sufficient time or because the diagnosis was missed, the end result being an atrophic testis. It is probable that we have identified the vast majority of cases of torsion of the spermatic cord occurring in Bristol over the last 25 years, although there may still be a few patients who have never consulted their doctor following an episode of acute scrotal pain.

The diagnosis of acute torsion was clear cut when the spermatic cord was found to be twisted within the tunica vaginalis at operation. Spontaneous resolution of torsion was diagnosed on the basis of unilateral testicular congestion usually with high investment of the tunica vaginalis and a reactive hydrocele. In a few patients with late torsion who were not explored there were obvious signs of testicular infarction. Recurrent torsion was diagnosed on the basis of episodic pain with evidence of an abnormally mobile testis at operation.

All relevant aetiological and clinical details were extracted from the case notes, and certain features were specifically identified: age, affected side, duration of hospital stay and surgical specialty responsible for the patient's care (i.e. general surgical, urological or paediatric). In addition, for the last 10 years the referral source was determined (usually either the general practitioner or the accident and emergency department) to indicate where any delay in treatment might originate.

It was sometimes difficult to determine the precise duration of symptoms. The duration of torsion was defined as the interval between onset of scrotal (or abdominal) pain and induction of anaesthesia. On occasion the patients' symptoms disappeared during this interval, and

Table 1 *Presentation of torsion of the spermatic cord*

	No. of cases
Acute torsion	539 (80)
Torsion in undescended testes	41 (6)
Late torsion	44 (7)
Recurrent torsion	46 (7)
Total	670

Percentages are given in parentheses

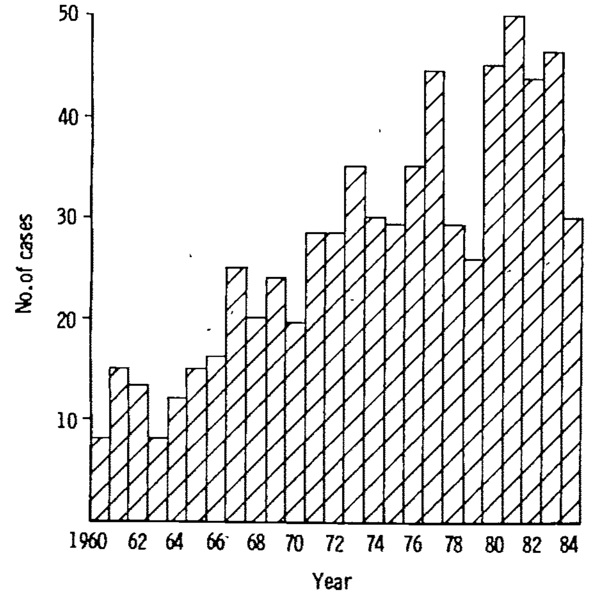


Figure 1 *Annual incidence of testicular torsion in Bristol 1960–84*

an approximation had to be made as to the probable duration of torsion. The testis was more frequently found to be untwisted at operation but still dusky, having presumably untwisted on anaesthetic induction. Among symptoms, particular note was taken of the site and radiation of pain, the presence of vomiting or urinary complaints and a history of previous similar attacks; any possible causative factors were also recorded. Among physical signs, temperature, the presence of a hydrocele or scrotal erythema and any abnormal disposition of the affected or contralateral testis were likewise obtained from the admission notes. Lastly, the surgeon's impressions of testicular viability and abnormal anatomy were gleaned from the operation note.

Results

Types of torsion (Table 1)

Of the 670 patients admitted there were 624 cases of proven testicular tosion. Among these, 41 (7 per cent) occurred in undescended testes, while 44 presenting at a late stage underwent elective operation, generally orchidectomy. Overall, 80 per cent had acute torsion of a scrotal testis. The remaining 46 patients received bilateral orchidopexy for recurrent episodes of short-lived testicular torsion.

Incidence

During the 25 years of the study, the annual incidence of torsion in Bristol increased nearly fourfold. Compared with the period 1960–64 (mean 11·2 cases per year), there were on average 42·8 cases per year with confirmed torsion of the spermatic cord between 1980 and 1984 (*Figure 1*). Since 88·5 per cent of cases occurred in patients <25 years of age, and there were c. 149 300 males in this age group in the Bristol area in June 1985 (Office of the Population and Census Studies, Department of Health and Social Security), the annual incidence of torsion over the last 5 years of the study was 1 case per 3942 males at risk. One in every 158 men will therefore have experienced torsion of the testis by the age of 25 years.

Age

Clustering of cases around puberty is confirmed in *Figure 2*. Of cases, 62 per cent occurred between the ages of 12 and 18 years, but torsion was as common among men in their twenties as it was among prepubertal children (12 and 14 per cent of all cases respectively). Overall, 20 per cent of cases of torsion occurred in men aged 21 years or more, and 6 per cent were aged 31 years or more.

The mean age at torsion was 16·7 years and the median age 15 years. The youngest patient seen with acute intravaginal testicular torsion was aged 9 days. The testis was undescended but viable. The oldest patient with torsion of the spermatic cord was aged 77 years. After antibiotic therapy for presumed epididymitis, testicular scintiscanning showed testicular infarction. Orchidectomy was required and the typical 'bell-clapper' deformity led to contralateral orchidopexy.

Side

Among 366 cases the left testis was affected, while in 304 torsion occurred on the right side. There was thus a 1·2:1 ratio in favour of the left side.

Predisposing factors

Anatomical abnormalities. Anatomical abnormalities of testicular fixation were commonly identified at operation. Among 331 patients seen between 1975 and 1984 with acute torsion of a scrotal testis, the anatomical findings were stated in 144 cases 75 had a high investment of the tunica vaginalis, 49 had a true 'bell-clapper' deformity while 13 had a long mesorchium between the epididymis and testis. The relevant abnormality was bilateral in all 40 patients in whom a description of the contralateral testis was available. The abnormalities of testicular fixation in these 144 patients were frequently associated with an abnormal lie of the contralateral testis at the pre-operative examination. This physical sign was recorded in 26 patients of whom 11 had a high investment of the tunica vaginalis at operation, 7 had the 'bell-clapper' anomaly and 1 had a long mesorchium. The abnormality was bilateral in every case.

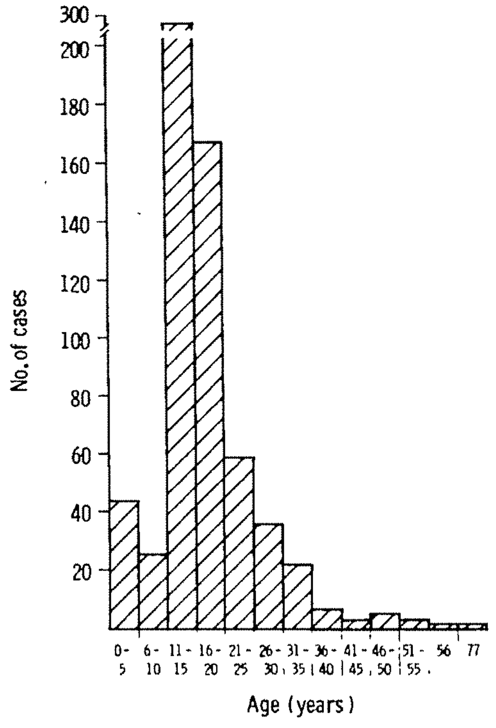


Figure 2 *Relative age incidence of testicular torsion in 670 patients*

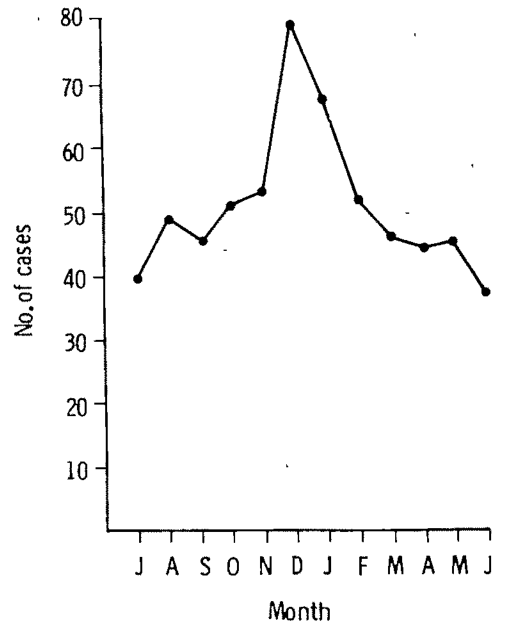


Figure 3 *Relative incidence of testicular torsion by month in 607 cases*

Table 2 *Symptoms of torsion*

Symptom	No. affected	
Pain		
Confined to scrotum	350/597 (59)	89%
Scrotal radiating to groin	45/597 (8)	
Scrotal radiating to abdomen	134/597 (22)	
Scrotal radiating to thigh	3/597	
Inguinal	36/597 (6)	
Abdominal	29/597 (5)	
Unable to say	27	
Urinary symptoms	26/556 (5)	
Vomiting	234/607 (39)	
Previous similar episodes	208/584 (36)	

Percentages are given in parentheses

Injury. A clear history of injury preceded the onset of torsion in 30 of the 670 cases (4 per cent). Similarly, a history of recent exercise was only reported in 47 patients (7 per cent). All sports were represented, but the commonest were football (10) and rugby (7). Bicycle riding was blamed in 12 patients (3 per cent) as the cause for torsion. Testicular torsion followed coitus in 4 patients. Strenuous activity is not a prerequisite for torsion. During the last 10 years of the review, 39 of 352 patients (11 per cent) with acute torsion were woken from sleep by scrotal pain. This group tended to be slightly younger overall (mean age 15·7 years).

Ambient temperature. To determine the effect of ambient temperature we studied the incidence of testicular torsion for each month of the year in 607 patients in whom this information was readily available. Our results confirm that torsion was more common during the cold months of the year, 24 per cent of the cases occurring during December and January (*Figure 3*). Statistical analysis of the data by a χ^2 test of goodness of fit showed a significant difference from a uniform distribution of cases over 12 calendar months ($\chi^2 = 30{\cdot}26$, d.f. = 11, $P < 0{\cdot}01$).

Family history. A family history of testicular torsion was only applicable in four patients. Two had a brother who had been treated for torsion in the past, while the fathers of two other patients had earlier experienced the same problem.

Symptoms (Table 2)

Scrotal pain was experienced by 89 per cent of patients. Half the remainder (33 of 65) had torsion of an undescended testis. Thus 32 of 597 patients (5 per cent) with a twisted but fully descended testis did not describe any scrotal pain. Isolated abdominal, suprapubic or loin pain was recorded in 5 per cent of cases, but in 22 per cent of the entire group scrotal pain was accompanied by abdominal pain which often preceded and sometimes exceeded the scrotal element. In three cases, all with accompanying vomiting, appendicitis was originally suspected, and the appendix was removed before the true diagnosis was made; only one of the three patients had a viable testis at definitive operation. Inguinal pain alone was described in 6 per cent of cases, while 8 per cent of patients had radiation of scrotal pain to the groin.

Urinary symptoms, typically slight frequency or dysuria, occurred in 5 per cent of cases. These patients tended to be younger than average (mean age 12·7 years) and often had testicular infarction (c. 60 per cent). Vomiting was a feature in 39 per cent of patients, and 36 per cent gave a past history of one or more attacks of unilateral or bilateral testicular pain and swelling.

Signs

Almost one-quarter of patients were reported to have an abnormal lie of the opposite testis on pre-operative examination. Secondary hydroceles were often recorded pre-operatively (52 per cent) and nearly always found at operation. Erythema and oedema of the overlying skin and a low-grade pyrexia were all associated with a longer duration of torsion and were thus of ominous import for the viability of the testis. Scrotal erythema was present in one-third of patients examined, and in all but 16 the duration of torsion exceeded 8 h. Pyrexia was seen in 16 per cent of patients, and half of these came to orchidectomy.

Mode of referral

During the final decade of the study, 240 of 352 patients with acute torsion (68 per cent) were initially seen by their general practitioner, while the remaining third were referred by the accident and emergency department. There was no correlation between the duration of symptoms and the mode of referral, and therefore it is unlikely that delay in treatment occurred for any reason other than the delay in the patients' initial presentation. The operative relief of torsion is usually undertaken by general surgeons. Until 1974, 95 per cent of cases were so treated. Thereafter 80 per cent of the 352 cases of acute torsion were managed by general surgeons, 13 per cent by specialist paediatric surgeons and 7 per cent (24 cases) by urological surgeons. There appears to be no change in this trend, with urologists seeing an average of two new cases per annum over the last 10 years. Those cases referred to urologists tend to represent a selected population, since 14 of the 24 required orchidectomy for prolonged torsion; the overall early salvage rate for those cases managed by urologists was only 42 per cent.

Operative findings

Manipulative reduction was successfully achieved in 12 patients overall and was always followed by expeditious surgery. At operation, 232 of 624 acutely twisted testes were found to be infarcted or gangrenous and another 6 were considered dead without the need for operation, giving an overall immediate testicular salvage rate of 62 per cent for the complete 25-year period (*Table 3*). There is a progressive improvement in this early salvage rate from 45 per cent in the years 1960–64 to 67 per cent for 1980–84, with a peak of 73 per cent between 1975 and 1979. It is interesting to note that the highest immediate testicular salvage rate coincides with the peak incidence of the diagnosis of torsion.

Overall, 44 patients (7 per cent) with prolonged torsion (>1 week) were admitted for elective contralateral orchidopexy with or without orchidectomy up to 3 months after the acute episode (*Table 4*). Two of those whose infarcted testis was not removed subsequently discharged the necrotic gland through the wound. Among the remaining 194 patients with an infarcted testis, 174 underwent immediate orchidectomy and contralateral orchidopexy; only one had immediate insertion of a prosthesis.

In the other 20 patients, orchidectomy was avoided despite the inevitable testicular infarction. Discharge of the necrotic testis through the wound occurred in 6 of 10 patients with detorsion and bilateral orchidopexy and 1 of 4 with contralateral orchidopexy alone. Likewise, in 4 of 6 patients in whom no operative procedure was performed, a discharging sinus developed from the necrotic testis. Thus, in 13 of 29 patients (45 per cent) the testis sloughed when attempts were made to preserve an obviously necrotic gland.

Duration of torsion and outcome

In 386 patients, the testis was preserved after either spontaneous or operative untwisting of the cord (*Table 3*). In 47 of these patients, all with symptoms of >10 h duration, there was some doubt concerning the viability of the testis. With a minimum follow-up of 3 months, 35 of these 47 patients had variable degrees of testicular atrophy, although no patient sloughed the testis through the wound (*Table 5*). Thus only 351 of 624 patients (56 per cent) had normal testes at least 3 months after acute torsion of the spermatic cord

The median duration of torsion in those with immediately non-viable testes was 48 h (range 4 h–15 days), although this figure had shortened to a median of 36 h (range 4 h–11 days) during the last decade. When testes of dubious viability were conserved but subsequently became atrophic, the median duration of torsion was 22 h (range 10–36 h). As expected, those testes considered fully viable were associated with a much shorter duration of torsion (median 5 h, range 1–36 h); this figure did not change throughout the period of study. Whenever the testis was viable despite prolonged symptoms, the extent of twist did not exceed 180° and had often resolved completely. Spontaneous resolution occurred in 46 of 352 patients (13 per cent) seen with acute torsion between 1975 and 1984.

Overall, if operation for acute torsion was performed within 12 h, only 4 per cent of affected glands were found to be non-viable. Beyond this time, loss of the testis became increasingly likely. Thus 75 per cent of patients had an infarcted testis with a duration of torsion >12 h, and another 11 per cent of patients were noted to have testicular atrophy if such a testis was conserved. After 12 h the chance of testicular survival depended on either spontaneous resolution or the degree of twist being limited to <360°.

Increased awareness of the condition has prompted earlier referral of patients for treatment. Between 1960 and 1974, <10 per cent of cases were seen before symptoms had been present for 4 h. Subsequently 15 per cent underwent operation within 3 h of the onset of symptoms, thus ensuring testicular survival in every case.

Postoperative complications

These were minimal and there were no deaths Apart from the 9 patients who discharged a necrotic testis through the wound following inappropriate retention of the gland, only 4 of the 377 patients operated on for torsion within the last 10 years developed a wound infection. One patient with sickle-cell anaemia suffered a chest infection. Another two had a recurrence of their torsion, as reported elsewhere[12]

Testicular maldescent

Torsion involved a maldescended testis in 41 of 670 cases (6 per cent). The 41 cases showed a similar left-sided preponderance to normally descended glands. The age ranged from 2 months to 34 years, with two-thirds occurring before puberty. Only five patients had had previous pain in the affected testis. Most presented with inguinal or abdominal pain, vomiting and a lump in the groin, which was readily mistaken for a strangulated hernia if the empty hemiscrotum had been overlooked. The salvage rate was predictably poor, 29 patients (71 per cent) coming to orchidectomy.

Recurrent subacute torsion

Over the last decade 25 patients have been treated for intermittent attacks of transient acute scrotal pain. This group differed from those requiring emergency operation. They were slightly older, with a median age of 21 years (range 10–47 years). Over half of them were treated by urological surgeons, and all underwent elective bilateral orchidopexy without complication. Their presenting symptoms were similar to those with acute torsion, but all had had multiple attacks of scrotal pain In 19 of the 25, the testis was said to have had a horizontal lie on the affected side and this finding was bilateral in 5 In 18 patients there was either a high investment of the tunica vaginalis or a 'bell-clapper' deformity at operation.

Discussion

The fourfold increase in incidence of testicular torsion during the 25 years of the present study must reflect a greater awareness of the condition among general practitioners and hospital

Table 3 *Early testicular salvage rates following acute torsion of the spermatic cord*

	Total no of cases	Viable testis at operation	Non-viable testis	Salvage rate (%)
1960–64	55	25	30	45
1965–69	91	48	43	53
1970–74	126	68	58	54
1975–79	156	114	42	73
1980–84	196	131	65	67
Overall	624	386	238	62

Table 5 *Fate of testis in relation to duration of symptoms*

Duration of symptoms (h)	*n* (%)	Viable at operation		
		Normal at follow-up	Atrophic at follow-up	Non-viable
0–6	226 (36)	222	—	4
7–12	99 (16)	88	1	10
13–18	27 (4)	16	3	8
19–24	58 (9)	18	10	30
25–48	62 (10)	3	13	46
>48	152 (24)	4	8	140
Total	624	351	35	238

Table 4 *Treatment and outcome in patients with testicular infarction*

Duration of symptoms	*n*	Orchidectomy	Contralateral orchidopexy only	No operation	Necrotic discharge
>1 week	44	35	9	0	2
<1 week	194	174	14	6	11
Total	238	209	23	6	13

doctors and an increasing readiness to explore any doubtful case. Furthermore, the entity of intermittent torsion is better recognized[13,14], so that surgeons are prepared to perform prophylactic orchidopexy in patients with episodic pain and undue testicular mobility. The diagnosis of 'non-specific epididymitis' in adolescents is rightly viewed with great supicion. The possibility of spontaneous reduction can make it difficult at operation to be certain that torsion has occurred, but usually the evidence is very suggestive. Doubtless as more of these resolved torsions are recognized, overall testicular viability figures will improve.

An apparent doubling in the frequency of undescended testis has been reported in England and Wales during the period 1962–81[15]. Although only 6 per cent of torsions involved undescended testes in the present review, other developmental abnormalities, in particular the so-called 'bell-clapper' deformity, may predispose to torsion in many cases. If both testicular maldescent and torsion of the testis are indeed becoming more common, it is possible that a common aetiological factor is responsible for the trends.

Torsion of the spermatic cord has been observed in every decade of life from infancy to 78 years[16]. However, it is predominantly a disease of adolescence and early adult life, the mean age in most reports being <18 years[3,4,6] and in the present series 16·7 years. Although more than two-thirds of cases occurred before the age of 18 years, the condition was not uncommon during the third decade of life (20 per cent of cases) and 6 per cent of patients were older than 30 years. Testicular torsion has previously been considered rare in men >30 years of age[17]. Our findings contradict this view, and, in one other series, 10 per cent of patients were >30 years of age[18]. One exceptional study from Nigeria reported 57 per cent of patients over the age of 20 years and 9 per cent over the age of 30 years[8]. Thus unilateral painful swelling of the testis in young men should not be assumed to be of infective cause without clear evidence in support[19].

Several reviews have shown a slight left-sided preponderance in testicular torsion[4,6,9,20], probably associated with the greater length of the left spermatic cord, and this is confirmed in the present series. However, since the anomaly predisposing to torsion is commonly bilateral, no great importance attaches to whichever side presents more frequently.

In patients with a high investment of the tunica vaginalis, any one of a large number of factors could cause cremasteric contraction and initiate torsion of the spermatic cord. Several such factors could be identified in the present study, but none were particularly prevalent. Life is marked by a succession of trivial injuries, and in the words of a *Lancet* editorial 'it is almost fatuous to name such pursuits as gardening or playing football as possible predisposing causes'[21]. Nevertheless our results support the view that there is an association between cold weather and the risk of testicular torsion[22–24], although agreement is not universal on this point[9].

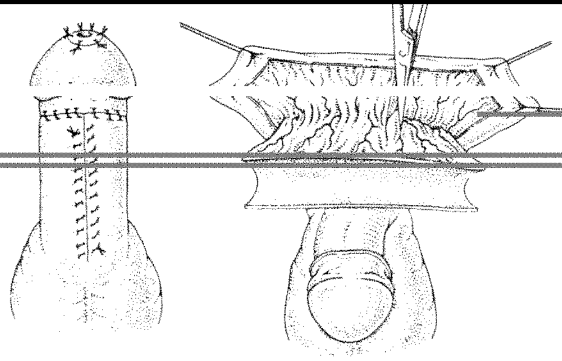
Over two-thirds of twisted testes are now saved from infarction by earlier referral and treatment (*Table 3*), a figure that compares with other recent reviews[9,25] and is a marked improvement on the 10 per cent reported by Barker and Raper in 1964[3]. The delay between the onset of symptoms and the time of operative reduction is of paramount importance for the immediate testicular salvage rate. Most testes can be saved if operated on within 12 h, but thereafter orchidectomy is necessary in 75 per cent of cases. Preservation of an infarcted testis carries a 45 per cent risk of suppuration, with a necrotic discharge that may require secondary orchidectomy. The duration of symptoms can only be a rough approximation to the chance of testicular viability. Other factors such as the degree of torsion and the 13 per cent possibility of spontaneous untwisting may play an equally important part in determining the testicular salvage rate.

While of some consolation to the patient affected by torsion, the late results of testicular preservation suggest that this is not the end of the story. Eight per cent of patients, all with symptoms of >10 h duration, had a 'viable' testis after untwisting of the cord but developed appreciable testicular atrophy at routine follow-up[29]. A close correlation has been demonstrated between the duration of torsion and the degree of testicular atrophy[26–29] Although torsion is being diagnosed more often and at an earlier stage, operative detorsion and orchidopexy cannot ensure normal testicular function, especially if the testis has been twisted for >10 h.

References

1. Hutchinson J. On acute atrophy of the testicle. *Arch Surg* 1895, **6** 100–2.
2. James T. Torsion of the spermatic cord in the first year of life *Br J Urol* 1953; **25**: 56–9
3. Barker K, Raper FR. Torsion of the testis *Br J Urol* 1964; **36**· 35–41.
4. Williamson RCN. Torsion of the testis and allied conditions *Br J Surg* 1976; **63**: 465–76
5. Coggon D, Nelms M Incidence of testicular abnormalities. *Lancet* 1984; **ii**· 747.
6. Skoglund RW, McRoberts JW, Ragde H. Torsion of the spermatic cord· a review of the literature and an analysis of 70 new cases. *J Urol* 1970; **104**: 604–7.
7. Cattolica EV, Karol JB, Rankin KN, Klein RS. High testicular salvage rate in torsion of the spermatic cord. *J Urol* 1982, **128**· 66–8
8. Udeh FN. Testicular torsion. Nigerian experience. *J Urol* 1985, **134**· 482–4.
9. Jones DJ, Macreadie D, Morgans BT. Testicular torsion in the armed services twelve year review of 179 cases. *Br J Surg* 1986, **73**· 624–6.
10. Donohue RE, Utley WLF. Torsion of spermatic cord. *Urology* 1978; **11**. 33–6
11. Cass AS, Cass BP, Veeraraghavan K. Immediate exploration of the unilateral acute scrotum in young male subjects. *J Urol* 1980; **124**: 829–32.
12. May RE, Thomas WEG Recurrent torsion of the testis following previous surgical fixation. *Br J Surg* 1980; **67** 129–30.
13. Sellu DP, Lynn JA Intermittent torsion of the testis *J R Coll Surg Edinb* 1984, **29** 107–8.
14. Stillwell TJ, Kramer SA. Intermittent testicular torsion *Pediatrics* 1986; **77**. 908–11.
15. Chilvers C, Pike MC, Forman D, Fogelman K, Wadsworth MEJ. Apparent doubling of frequency of undescended testis in England and Wales. *Lancet* 1984, **ii**: 330–2.
16. O'Conor VJ. Torsion of the spermatic cord and torsion of the hydatid testis. *Med Clin N Am* 1959; **43**. 1731–6.
17. Altaffer LF. Testicular torsion in men. *J Urol* 1980; **123**: 37–8.
18. Lee LM, Wright JE, McLoughlin MG. Testicular torsion in the adult *J Urol* 1983; **130**· 93–4.
19. Jones HO. Leave no stone unturned. *J Med Def Union* 1986; **2**: 21.
20. Williams JD, Hodgson NB Another look at torsion of testis. *Urology* 1979; **14** 36–8.
21. Editorial. The twist of the cord. *Lancet* 1958; **i** 725–6.
22. Shukla RB, Kelly DG, Daly L, Guiney EJ. Association of cold weather with testicular torsion. *Br Med J* 1982, **285**. 1459–60
23. Williamson RCN. Cold weather and testicular torsion. *Br Med J* 1983; **286**: 1436
24. Newcombe RG Cold weather and testicular torsion. *Br Med J* 1983; **287**. 359
25. Goulbourne IA, Nixon SJ, Macintyre IMC. Computer aided diagnosis in acute testicular pain. *Br J Surg* 1984, **71** 528–31
26. Krarup T. The testes after torsion *Br J Urol* 1978, **50**: 43–6.
27. Bartsch G, Frank S, Marberger H, Mikuz G. Testicular torsion: late results with special regard to fertility and endocrine function. *J Urol* 1980; **124**· 375–8.
28. Thomas WEG, Cooper MJ, Crane GA, Lee G, Williamson RCN. Testicular exocrine malfunction after torsion. *Lancet* 1984; **ii**: 1357–60.
29. Anderson JB, Williamson RCN. The fate of the human testes following unilateral torsion of the spermatic cord. *Br J Urol* 1986, **58**: 698–704

[redacted]



advice for all surgeons who operate on children. It continues to be an indispensable companion to paediatric surgical practice.

Contents: Transport of surgical neonate · Pre- and postoperative management · Paediatric anaesthesia · Head and Neck · Thorax · Abdominal wall · Gastrointestinal tract · Liver and portal system · [illegible] Limbs · Trauma · Index.

September 1988 700 pages 276 x 219mm Hardcover
Illustrated
0 407 006664 £160.00

Order this title from your usual bookseller or complete the coupon below.

ORDER FORM

To: **Butterworths & Co (Publishers) Ltd, Borough Green, Sevenoaks, Kent TN15 8PH, England. Telephone: (0732) 884567 Telex: 95678.**

24 Hour Order Line: (0732) 882566 – This line gives immediate access at any hour. Orders can be placed over the telephone by using your Butterworths account number or by charging to your credit account.

Cash or credit card details with order are essential except for account customers. Overseas orders not accompanied by a remittance will be charged postage and packing.

Please send me copy(ies) of **Rob and Smiths Operative Surgery – Paediatric Surgery** 0 407 00666 4 @ £160.00

Please select preferred method of payment:

☐ I enclose remittance for £ ....

☐ Please debit my credit card as follows

☐ Access/Mastercard ☐ Barclaycard and other
☐ American Express Visa cards

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry Date ____________ Signature ____________

☐ Please include me on your mailing list

Name ____________

Position ____________

Address ____________

____________ Postcode ____________

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. In the UK please allow 21 days for delivery.

Registered office: 88 Kingsway, London, WC2B 6AB
Registered in England No 125354

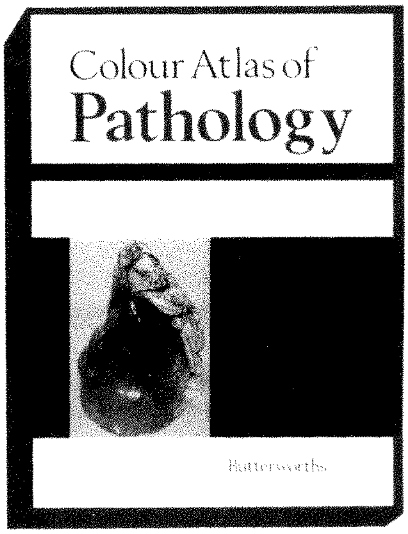
Butterworths
meeting professional needs

BOROUGH GREEN SEVENOAKS KENT TN15 8PH UK

BUTTERWORTHS PATHOLOGY . . .

Colour Atlas of Pathology

Luigi Giarelli, MD
Professor and Chairman
Mauro Melato, MD
Associate Professor
Guglielmo Antonutto, MD
Associate Professor, Istituto di Anatomia e Istologia Patologica, University of Trieste, Trieste, Italy
English translation by
Ettore De Girolami, MD
Clinical Professor of Pathology, University of Miami Medical School; Senior Pathologist, South Miami Hospital, Miami, Florida, USA
with nine contributing translators
Butterworths edition revised by
I A Ellis, J S Lowe
and members of the Department of Pathology, University Hospital, Queen's Medical Centre, Nottingham, UK



- ★ **More than 1300 excellent colour illustrations**
- ★ **Excellent value at £50**
- ★ **Illustrates gross pathology and histopathology**
- ★ **Concise introductory text**
- ★ **For all pathologists, in practice or training**
- ★ **Ideal reference for MRC Path and FRCS**

Contents: Mouth, upper digestive and respiratory tract ● **Respiratory system** ● **Digestive system:** Oesophagus ● Stomach ● Intestine ● Liver ● Extrahepatic bile ducts and gallbladder ● Pancreas (exocrine) ● **Urogenital system:** Kidney ● Lower urinary tract, ureter, bladder, urethra ● Prostate ● Seminal vesicles ● Testes, epididymis, and testicular adnexal structures ● Ovary ● Uterine (fallopian) tubes ● Uterus ● Vagina ● **Endocrine system** ● **Nervous system** ● **Osteoarticular system** ● **Cardiovascular and haemopoietic systems:** Heart ● Blood vessels ● Haemopoietic system ● **Skin, adnexa, and soft tissues** ● **Diseases with multiple system involvement** ● **Index**

1987 736 pages 280 x 210 mm Hardcover Colour Illustrations 0 407 00301 0 £50.00

Order from your usual bookseller – or in case of difficulty from Butterworths using the coupon below.

Order Form

Please return to Judy Chappell, Butterworths, PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK.

☐ Please send me ________ copy(s) of **Colour Atlas of Pathology** 0 407 00301 0 at £50.00 each

☐ Please send me more information on Butterworths forthcoming Pathology titles

Cash or credit card details with order are essential for account customers.
Please select preferred method of payment

☐ I enclose remittance for £ ....
Cheque made payable to Butterworth & Co (Publishers) Ltd

☐ Please debit my credit card as follows:

☐ Access/Mastercard ☐ Barclaycard and other VISA cards ☐ American Express

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry date ....

Signature .... Date ....

Name ....

Position ....

Address ....

....

.... Postcode ....

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. Please allow 21 days for delivery in the UK.

Registered Office: 88 Kingsway, London WC2B 6AB
Registered in England No 125354

Butterworths
meeting professional needs

Br. J. Surg. 1988, Vol. 75, October,
993–996

Anal sensation after restorative proctocolectomy for ulcerative colitis

The hypothesis that anal sensation might be better after restorative proctocolectomy with end-to-end ileoanal anastomosis than after mucosal proctectomy with endo-anal anastomosis was tested in this study. Anal sensation was measured in 14 patients before operation, 16 patients after restorative proctocolectomy with end-to-end anastomosis (RP + EEA) and 13 patients after mucosal proctectomy with endo-anal anastomosis 1 cm above the dentate line (MP + EAA). Threshold electrosensitivity was measured in the upper, mid and lower anal canal by means of a bipolar constant current stimulator probe. The 'recto'-anal inhibitory reflex was tested, and the patients' ability to discriminate between flatus and faeces and to release flatus 'safely' was assessed by interview. In the upper anal canal, threshold sensitivity was significantly greater in patients who had undergone MP + EAA than in patients who had undergone RP + EEA ($P<0{\cdot}05$)*. In the mid and lower anal canal, electrosensitivity in the three groups of patients did not differ significantly. Twelve patients (75 per cent) regained the 'recto'-anal reflex after RP + EEA, but after MP + EAA only three patients (23 per cent) did so* ($P<0{\cdot}02$)*. Thirteen patients after RP + EEA could release flatus safely without fear of faecal leakage, compared with only four after MP + EAA* ($P<0{\cdot}02$)*. The proportions of patients in these two groups who said they were able to discriminate flatus from faeces did not differ significantly. Anal sensation and discriminatory function are significantly better after end-to-end ileoanal anastomosis than after mucosal proctectomy with endo-anal anastomosis.*

Keywords: Anus, ulcerative colitis, proctocolectomy, sensation

P. J. Holdsworth and
D. Johnston

University Department of Surgery,
The General Infirmary, Great
George Street, Leeds LS1 3EX, UK
Correspondence to:
Professor D. Johnston

The sensory nerve supply of the anal canal was described in detail by Duthie and Gairns in 1960[1]. In a subsequent paper Duthie and Bennett postulated that the sensory anal mucosa, particularly in the region of the transitional zone above the dentate line, permitted 'sampling' of rectal content when the internal sphincter relaxed in response to rectal distension[2]. Thus the sensory zone in the upper anal canal and the recto-anal inhibitory reflex together enable us to discriminate between solid, liquid and gas and thus play a major part in the fine control of continence[3,4].

In the course of standard mucosal proctectomy for ulcerative colitis, in which an endo-anal ileoanal anastomosis is constructed at the dentate line (*Figure 1*), the sensitive mucosa of the upper anal canal is stripped away, to be replaced by the outflow tract of the pelvic ileal reservoir. Loss of this important sensory zone might be expected to lead to imperfections in anal discriminatory function and perhaps to leakage of flatus or faeces. Indeed, an increase in mucosal threshold electrosensitivity in the mid and upper anal canal—suggestive of impaired sensation—was reported recently after endo-anal anastomosis at the dentate line: such changes were not observed in two patients in whom the anal transitional zone had been preserved[5].

We showed previously that the anal transitional zone was relatively spared from the inflammatory process of ulcerative colitis[6]. Our hypothesis was that anal sensory function would suffer less damage if the anal canal was preserved intact in the course of restorative proctocolectomy for colitis (*Figure 2*) than if the anal mucosa was stripped above the dentate line. Such preservation of anal sensation might be expected to improve the quality of life for patients who undergo this type of operation, and should complement the well-preserved motor function of the anal sphincter that we described previously after this operation[7].

Patients and methods

A total of 14 patients with ulcerative colitis before operation, 16 patients after end-to-end ileoanal anastomosis and 13 patients after endo-anal ileoanal anastomosis performed approximately 1 cm above the dentate line (*Figure 3*) were studied (*Table 1*). Details of the operative techniques used in the construction of the end-to-end and endo-anal anastomoses have been described previously[7–10]. In each patient, threshold electrosensitivity of the mucosa of the anal canal was measured by means of a bipolar constant current stimulator probe lubricated with a solution of K-Y jelly (Johnson and Johnson) and normal saline in equal quantities[11]. Electrosensitivity was measured in the upper, mid and lower anal canal as defined by anal manometry. The recto-anal inhibitory reflex was assessed in all patients by inserting a balloon catheter into the rectum or neo-rectum, taking care that the lower border of the balloon was at least 10 cm above the anal verge. Pressure in the anal canal was measured at the site of maximum resting anal pressure using a water filled microballoon manometry system. To initiate the reflex the rectal balloon was inflated with air in 10 ml increments and the recto-anal inhibitory reflex was said to be present if resting anal

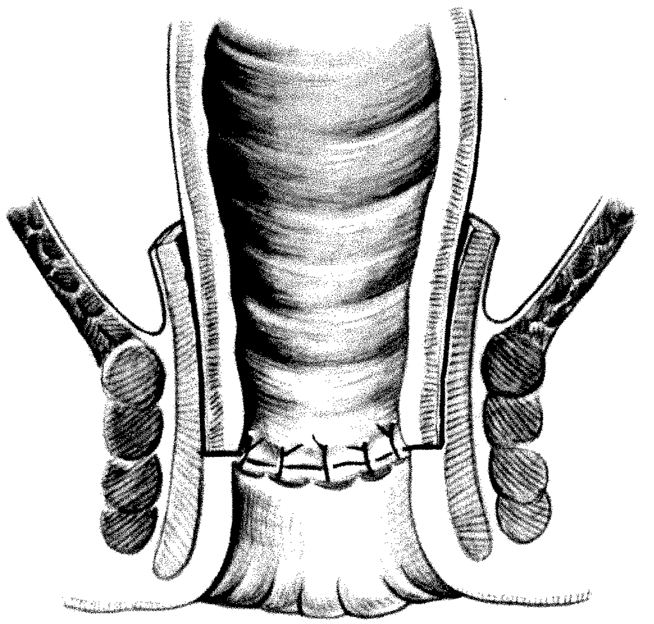


Figure 1 *Endo-anal ileoanal anastomosis at the dentate line after mucosal proctectomy*

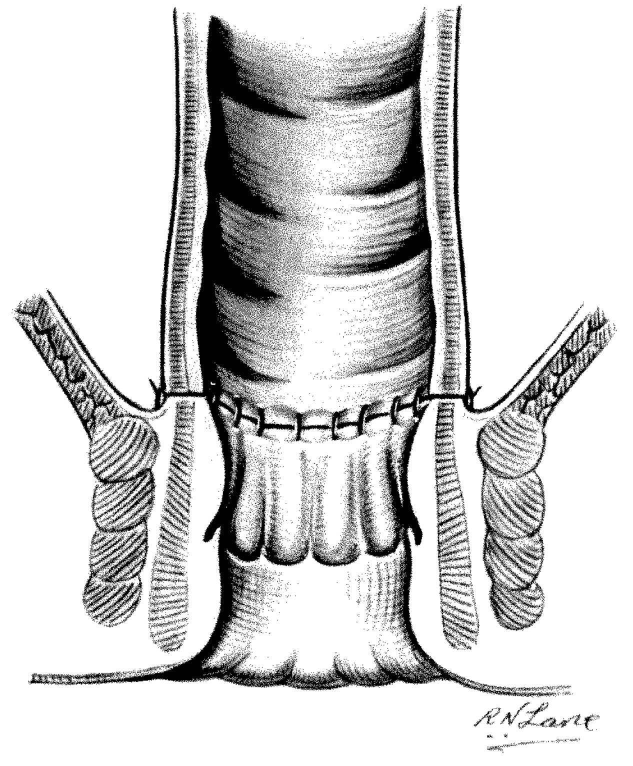


Figure 2 *Stapled end-to-end ileoanal anastomosis at the level of puborectalis*

pressure decreased by more than 20 per cent in response to rectal distension (*Figure 4*).

The patients were interviewed individually by one author (P.J.H.) and their ability to discriminate between flatus and faeces was assessed, as was their ability to release flatus safely without having to visit the lavatory. The latter function was felt to provide a more accurate indicator of anal discriminatory function than does the mere ability to 'discriminate'.

Statistical analysis

The results were expressed as medians and interquartile ranges unless otherwise stated. Data from different groups were compared using the Mann–Whitney *U* test and Fisher's exact test[12].

Results

In the upper anal canal, threshold mucosal electrosensitivity of the patients after end-to-end anastomosis, median 7·9 mA (4·5–10·0 mA), did not differ significantly from that of patients before operation, median 7·3 mA (5·4–7·8 mA) (P = n.s.). However, patients who had undergone mucosal proctectomy and endo-anal anastomosis had a significantly higher threshold, median 9·1 mA (7·4–17·3 mA), than patients before operation ($P < 0{\cdot}05$).

In the mid and lower anal canal, there was no significant difference between sensory thresholds of pre-operative patients, (4·5 mA (3·4–5·2 mA) and 5·7 mA (3·5–6·2 mA) respectively), patients after end-to-end anastomosis (5·8 mA (3·5–6·4 mA) and 4·5 mA (4·0–6·0 mA) respectively) and patients after endo-anal anastomosis (4·2 mA (3·4–6·1 mA) and 4·0 mA (2·7–4·7 mA) respectively) (*Figure 5*).

The clinical results are shown in *Table 2*. Before operation, all patients were able to discriminate flatus from faeces and to release flatus safely, and each patient had a demonstrable recto-anal inhibitory reflex. After operation, each of 16 patients in whom an end-to-end anastomosis had been performed were able to discriminate flatus from faeces, whereas only 77 per cent of patients who had undergone endo-anal anastomosis were able to do so (P = n.s.).

After end-to-end anastomosis, a significantly greater proportion of patients (81 per cent) felt confident to release flatus without fear of leakage, compared with the proportion of

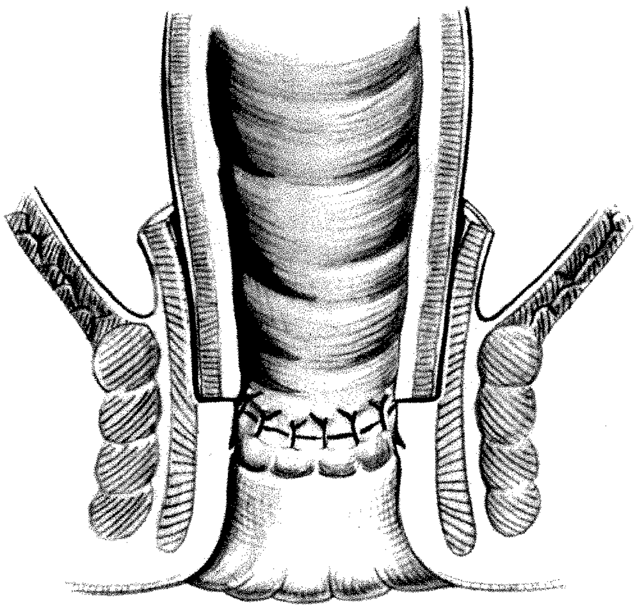


Figure 3 *Endo-anal ileoanal anastomosis 1 cm above the dentate line*

Table 1 *Details of patients*

	Before operation	End-to-end anastomosis	Endo-anal anastomosis
Number	14	16	13
Age (years)*	32 (25–40)	44 (31–53)	36 (27–38)
Follow-up (months)*	—	10 (8–14)	42 (30–52)
M:F ratio	7:7	9:7	9:4
Pouch			
Triplicated	—	10	4
Duplicated	—	0	7
Straight	—	6	2

* Median (interquartile range)

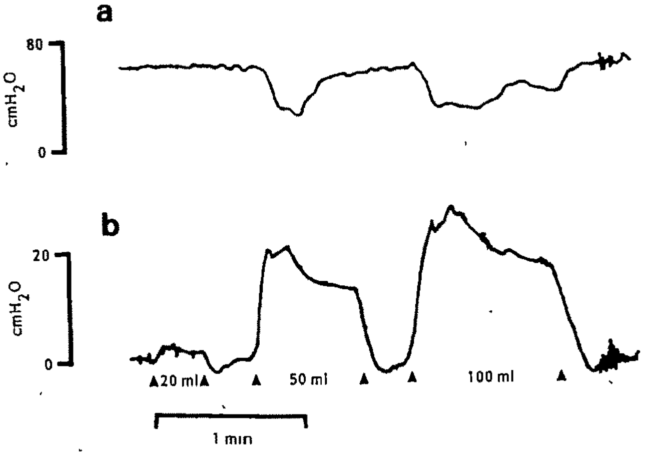


Figure 4 *The 'recto'-anal reflex after end-to-end ileoanal anastomosis, showing anal relaxation in response to inflation and deflation of a balloon in the neo-rectum* (▲). **a**, *Anal pressure*; **b**, *neo-rectal pressure*

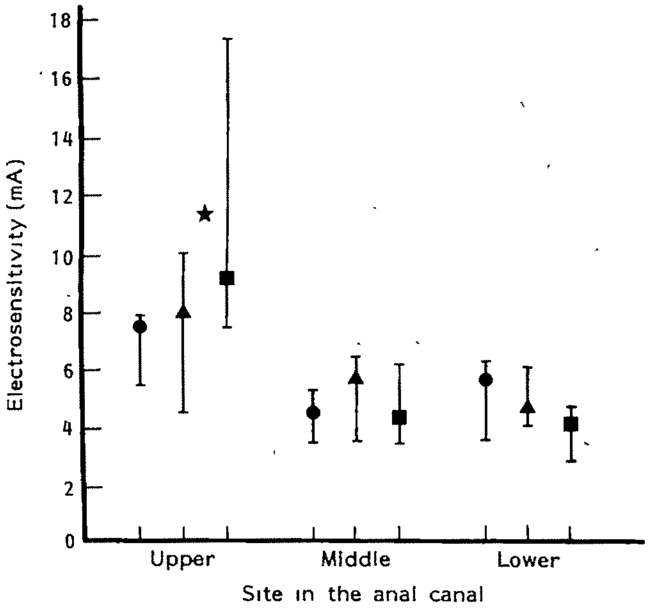


Figure 5 *Threshold electrosensitivity in the upper, mid and lower anal canal in patients before operation* (●), *patients after end-to-end ileoanal anastomosis* (▲) *and patients after endo-anal anastomosis* (■), *expressed as median and interquartile range* (* $P < 0\cdot05$)

patients (31 per cent) who could do so after endo-anal anastomosis ($P < 0\cdot02$). The 'recto'-anal inhibitory reflex was present in 75 per cent of patients after end-to-end anastomosis, but in only 23 per cent of patients after endo-anal anastomosis ($P < 0\cdot02$). Of patients who were able to release flatus 'safely', 80 per cent had regained the 'recto'-anal inhibitory reflex, whereas only 36 per cent of patients who were unable to release flatus 'safely' had regained the reflex ($P < 0\cdot05$).

Discussion

Measurement of threshold mucosal electrosensitivity in the anal canal in this study showed that formation of an end-to-end ileoanal anastomosis did not impair sensitivity to a significant extent at any site in the anal canal. In contrast, significant blunting of sensation was found in the upper anal canal of patients who had undergone endo-anal anastomosis. This may be related to the stripping of ano-rectal mucosa and its replacement by ileal mucosa in this segment of the anal canal. We did not observe the large reduction in electrosensitivity in the mid-anal canal that has been described by Keighley *et al.* after endo-anal anastomosis performed at the dentate line[5]. The most likely explanation for the disparity between Keighley's findings and ours is that in Keighley's patients mucosal stripping began at the dentate line, whereas in our patients who underwent mucosal proctectomy and endo-anal anastomosis approximately 1 cm of anal transitional mucosa was retained above the dentate line (*Figure 3*).

Table 2 *Clinical results after two methods of ileoanal anastomosis*

	End-to-end anastomosis (%)	Endo-anal anastomosis (%)	P*
Ability to discriminate faeces from flatus	100	77	n.s.
'Recto'-anal reflex present	75	23	<0·02
'Safe' release of flatus	81	31	<0·02

* Fisher's exact test

After both types of anastomosis, most patients said that they were able to discriminate between flatus and faeces. Nevertheless, we felt that the patients' ability to discriminate would be most accurately reflected by his or her ability to release flatus safely without fear of faecal leakage. There is, presumably, no great advantage in being able to discriminate between flatus and faeces if the patient still has to visit the lavatory in order to pass flatus. The higher proportion of patients who were able to release flatus normally following end-to-end anastomosis, compared with the proportion who could do so after endo-anal anastomosis, may be reflected in a lower bowel frequency, although we appreciate that the two groups of patients are not accurately matched with regard to other factors, such as pouch design and length of follow-up, which are known to influence bowel frequency[10,13].

Our findings suggest that the ability to release flatus safely is associated with recovery of the 'recto'-anal inhibitory reflex. As that reflex is mediated by the intramural nerve plexus, this implies that there is growth of intramural nerves across the ileoanal anastomosis[14,15]. If that is the case, our results suggest that such nerve regeneration occurs significantly more often after end-to-end anastomosis than after endo-anal anastomosis. This would appear plausible on anatomical grounds, because regeneration seems less likely to take place across an endo-anal 'sleeve' anastomosis than an end-to-end anastomosis.

In this study, we have shown that preserving the entire anal canal, without mucosal stripping or endo-anal anastomosis, has distinct advantages for the patient, with respect to sensory function of the anal sphincter. The maintenance of anal sensitivity, in combination with the excellent anal motor function that we described previously after end-to-end anastomosis, has resulted in better overall anal function in patients after restorative proctocolectomy[7]. Martin *et al.* also commented on the advantages of preserving the mucosa of the anal transitional zone, but in their series colitis recurred in 6 out of 12 patients in whom too much ano-rectal mucosa had been preserved above the dentate line[16]. Similar problems could arise in patients who have undergone end-to-end ileoanal anastomosis. To date, however, no clinical evidence of recurrent colitis has been found and we believe that the advantages—both technical and physiological—of preserving the entire anal canal outweigh the possible disadvantages.

References

1. Duthie HL, Gairns FW. Sensory nerve endings and sensation in the anal region of man. *Br J Surg* 1960; **47**: 584–94
2. Duthie HL, Bennett RC The relation of sensation in the anal canal to the functional anal sphincter. a possible factor in anal continence. *Gut* 1963, **4**: 179–82.
3. Miller R, Bartolo DCC, Cervero F, Mortensen NJMcC. Ano-rectal sampling: a comparison of normal and incontinent patients. *Br J Surg* 1988; **75**: 44–7.

4 Gowers WR. The automatic function of the sphincter ani. *Proc R Soc Lond* 1877; **26**: 77–84.

5. Keighley MRB, Winslet MC, Yoshioka K, Lightwood R. Discrimination is not impaired by excision of the anal transitional zone after restorative proctocolectomy. *Br J Surg* 1987; **74**: 1118–21.

6. Deasy JM, Quirke P, Dixon MF, Lagopoulos M, Johnston D. The surgical importance of the anal transitional zone in ulcerative colitis (abstract). *Br J Surg* 1987; **74**: 533.

7. Johnston D, Holdsworth PJ, Nasmyth DG *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. *Br J Surg* 1987; **74**: 940–5.

8. Neal DE, Williams NS, Johnston D Rectal, bladder and sexual function after mucosal proctectomy with and without a pelvic ileal reservoir for colitis and polyposis. *Br J Surg* 1982; **69**: 599–604.

9. Johnston D, Williams NS, Neal DE, Axon ATR. The value of preserving the anal sphincter in operations for ulcerative colitis and polyposis. a review of 22 mucosal proctectomies. *Br J Surg* 1981; **68**: 874–8.

10. Nasmyth DG, Johnston D, Godwin PGR, Dixon MF, Smith A, Williams NS. Factors influencing bowel function after ileal pouch-anal anastomosis. *Br J Surg* 1986; **73**: 469–73.

11. Roe AM, Bartolo DCC, Mortensen NJMcC. New method for assessment of anal sensation in various ano-rectal disorders. *Br J Surg* 1986; **73**: 310–12.

12. Cohen L, Holliday M. *Statistics for Social Scientists*. London: Harper and Row, 1982.

13. Primrose JN, Holdsworth PJ, Nasmyth DG, Womack N, Neal DE, Johnston D. Intact anal sphincter with end-to-end ileo-anal anastomosis for ulcerative colitis: comparison with mucosal protectomy and pull-through anastomosis (abstract). *Br J Surg* 1987; **74**: 539

14. Lubowski DZ, Nicholls RJ, Swash M, Jordan MJ. Neural control of internal sphincter function. *Br J Surg* 1987; **74**: 668–70.

15. Lane RHS, Parks AG. Function of the anal sphincter following colo-anal anastomosis. *Br J Surg* 1977; **64**. 596–9.

16. Martin LW, Torres AM, Fischer JE, Alexander F. The critical level for preservation of continence in the ileo-anal anastomosis. *J Pediatr Surg* 1985; **20**: 664–7

The Cutlers' Prize

Each year the specialist surgical associations, in conjunction with the Royal College of Surgeons of England, choose a person (or team) who has performed outstanding work or achieved a significant advance in design or clinical practice in the field of instrumentation or technical development in any branch of surgery. The person selected is recommended to the Worshipful Company of Cutlers for approval and for the award of the Cutlers' Prize.

Applications are now invited for the 1989 award. Each application should be submitted on the form provided and should be in regard to one specific instrument. The claim to originality of conception, design or manufacture must be substantiated and details given of any patent. An application can be in regard to a modification to an instrument currently in use, but it must be a *major* modification.

Ten copies of a typed or printed abstract detailing the design, date of development, clinical use and merits of the instrument or technique, illustrated by scale drawings and/or photographs, and explaining the benefits to patient care, should be sent to:

The Honorary Secretary
The Association of Surgeons of Great Britain and Ireland
The Royal College of Surgeons of England
35/43 Lincoln's Inn Fields
London WC2A 3PN
UK
Telephone number 01 405 6753

The closing date for the receipt of applications is 31 October 1988.

Br. J. Surg. 1988, Vol. 75, October, 997–1002

Physiological parameters influencing function in restorative proctocolectomy and ileo–pouch–anal anastomosis

M. R. B. Keighley,
K. Yoshioka,
W. Kmiot and
F. Heyen

The General Hospital, Birmingham, UK

Correspondence to:
Professor M. R B. Keighley,
The Clinical Teaching Block,
General Hospital,
Birmingham B4 6NH, UK

Ileo–pouch–anal function has been assessed in 30 patients after restorative proctocolectomy and compared with age- and sex-matched controls. Median resting anal canal pressure was only 42 cmH_2O (7–113 cmH_2O) compared with 100 cmH_2O (46–114 cmH_2O) in controls ($P < 0.005$). *Maximum squeeze anal pressures were also significantly lower in pouch patients: 87 cmH_2O (25–180 cmH_2O) than controls: 143 cmH_2O (114–171 cmH_2O)* ($P < 0.01$). *The recto-anal inhibitory reflex was absent in all pouch patients but was present in all controls. Maximum pouch or ileal pressures exceeded resting anal canal pressures in three patients. Median volume at first leak during saline infusion was 320 ml (60 ml–no leak) in pouch patients whereas the majority of controls had no leakage (median, none; 450 ml–no leak;* $P < 0.05$). *Threshold pouch sensation (median, 50 ml (0–250 ml)) did not differ from rectal sensation in controls (50 ml (0–180 ml)) but pouches were less compliant than a normal rectum, median 6·8 ml/cmH_2O (2·1–17 ml/cmH_2O) and 11·6 ml/cmH_2O (4·7–16·2 ml/cmH_2O) respectively* ($P < 0.05$). *In patients who had an episode of pelvic sepsis* ($n = 8$) *the average number of abnormal physiological indices per patient was 3·8, compared with 1·3 in those with no sepsis* ($P < 0.05$). *There was no difference in the number of abnormalities per patient with a J pouch (2·0;* $n = 19$*) or a W pouch (1·9;* $n = 11$*).*

Keywords: Restorative proctocolectomy, anal pressure, ileal pouch pressure, anal sensation, pouch sensation

Hitherto, most physiological studies of patients after restorative proctocolectomy have been confined to anal pressure measurement[1,2] and pouch capacity or compliance[3,4]. Almost without exception, resting anal pressures fall after restorative proctocolectomy whereas the voluntary component is often uninfluenced[5]. We have shown that the fall in resting anal pressure can be minimized by avoiding excessive anal retraction[6]. Compliance and capacity are greater with the three-lumen or four-lumen pouch compared with a two-lumen J pouch[7] However, it is becoming apparent that there are many other motor factors which influence pouch function, particularly small bowel transit, bacterial overgrowth and pouch emptying[8,9]. On the afferent side of the defaecatory mechanism, pouch and anal sensation appear to be dependent upon the extent of the abdominal mucosectomy[10,11]

The aim of this study was to assess simultaneous ileal pouch and anal pressures, pouch anal sensation, and saline infusion after restorative proctocolectomy compared with controls. We also wish to define the incidence of physiological abnormalities with respect to pouch design, sepsis, duration of follow-up and functional results.

Patients and methods

Thirty patients operated upon in this institution between 1983 and 1987 having restorative proctocolectomy with a J ($n = 19$) or a W ($n = 11$) pouch were studied. All patients were evaluated in January and February 1988 by one person (W.K) who was unaware of the type of pouch used for reconstruction The duration of follow-up was 28 months (range 6–55 months). A functional score ranging from 0 to 12 was derived from the following the frequency of defaecation (>5 stools/day or >1/night); inability to defer defaecation for >1 h, soiling of underwear rather than incontinence during the day or at night; the wearing of pads (day or night), true incontinence, failure to discriminate between gas and solid; dietary restriction, and continued use of antidiarrhoeal agents (*Table 1*). Patients were subdivided into two groups, those with a score of 3 or more signifying an imperfect functional outcome and the remainder with minimal functional disturbance having a score of 0–2 Seven patients had scores of 3 or more In eight patients there had been a previous episode of pelvic sepsis attributable to a

Table 1 *Derivation of functional score*

Factor	Score
Stool frequency >5 during the day	1
Stool frequency >7 during the day	1
Stool frequency >1 during the night	1
Inability to defer defaecation >1 h	1
Soiling in the day	1
Soiling at night	1
Wearing of pads in the day	1
Wearing of pads at night	1
True incontinence	1
Failure of discrimination	1
Dietary restriction	1
Antidiarrhoeal agents used	1

0007-1323/88/100997-06$3 00

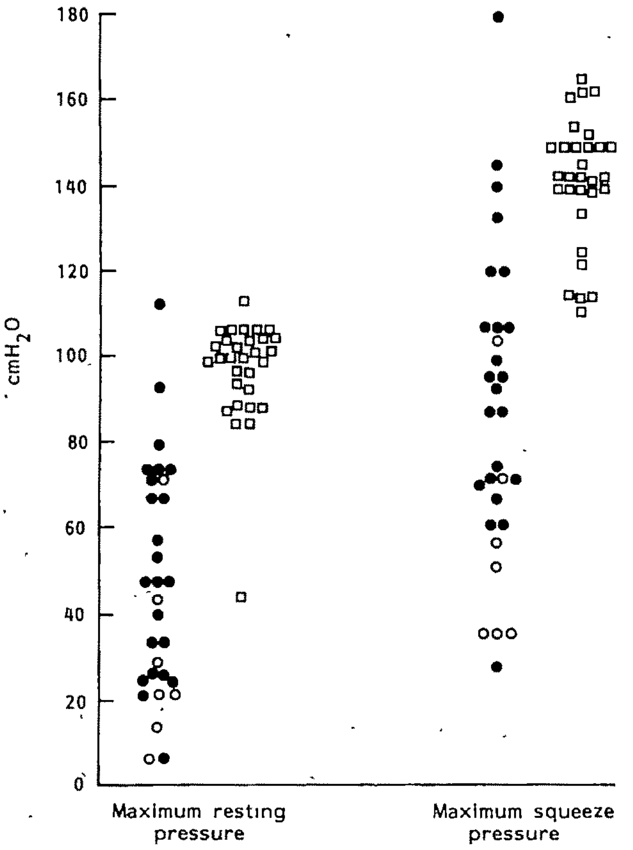


Figure 1 *Maximum resting* (P<0·005) *and maximum squeeze* (P<0·01) *anal pressure* (cmH$_2$O) *after restorative proctocolectomy compared with controls.* ●, *Patients with good function,* ○, *patients with poor function;* □, *controls*

contained leak or an infected pelvic haematoma. None of these patients had persistent sepsis at the time of study. Results in pouch patients were compared with a group of previous controls who were matched with the patients for age and sex and who did not have any evidence of anorectal disease. The control data have been collected over the two preceding years using exactly the same physiological parameters with the same infusion catheters and manometry equipment identical to that employed in the present study.

Simultaneous ileal pouch and anal pressures were recorded using a four-lumen catheter (5 mm diameter) perfused with sterile water at a rate of 0·5 ml/min with side arms at 2, 6, 10 and 20 cm from the anal verge[12]. The perfusion system incorporated an Arndorfer large-volume infusion pump connected to transducers and a multichannel pen recorder. The position of the catheter was checked fluoroscopically in 10 patients. Earlier validation studies had identified the manometric characteristics of a kinked catheter and we were satisfied that the tip of the catheter lay in the terminal ileum. Measurements were taken in the left lateral and seated positions Basal pressures were recorded over 10 min. Changes following maximum pelvic floor contraction and attempted defaecation were also observed. Serial 20 ml increments of air were then introduced into a balloon situated in the centre of the pouch to a maximum of 180 ml over 10 min. Pressures in the anal canal and proximal ileum in response to pouch distension were recorded, as well as the changes in intraballoon pressure in order to measure pouch compliance. Pouch sensation was assessed by recording threshold volume (transient desire to defaecate) and constant volume (constant feeling of impending defaecation) using the criteria of Farthing and Lennard-Jones[13]. Anal sensation was measured using our own monopolar constant-current stimulator to assess threshold mucosal sensitivity in the lower, mid and upper anal canal as previously described[10].

A separate two-lumen catheter (5 mm diameter) was used for the saline infusion test with side holes at 2 and 6 cm After the catheter had been taped securely into position, the patient was seated on a commode under which was a metal receiver. Saline was infused into the pouch through the end of the catheter (10 cm from the anal verge) while simultaneous recordings were made of anal and pouch pressure. Episodes of leakage were identified by a rise in pouch pressure associated with a profound fall in anal pressure and an audible discharge of liquid into the receiver Infusion was at a rate of 50 ml/min to a total volume of one litre. Analysis was confined to the measurement of the volume at first leak of saline and total retained volume (recorded as a percentage of volume infused which did not leak from the pouch or rectum). The numerical data were not normally distributed and were therefore analysed using the Mann-Whitney *U* test

Results

The median resting anal pressure (42 cmH$_2$O; 7–113 cmH$_2$O) was significantly lower than that of the controls (100 cmH$_2$O; 46–114 cmH$_2$O; $P<0{\cdot}005$). Six of the seven patients with an imperfect result had resting anal pressures that were less than the median value (*Figure 1*). The median resting anal pressure in seven patients with imperfect function was only 21 cmH$_2$O (7–67 cmH$_2$O) compared with a median value of 54 cmH$_2$O (8–113 cmH$_2$O) in the remainder ($P<0{\cdot}001$). The median resting anal pressure in the eight patients with pelvic sepsis was 29 cmH$_2$O (7–73 cmH$_2$O) compared with 55 cmH$_2$O (7–113 cmH$_2$O) in those who had no sepsis ($P<0{\cdot}005$). However, there was no difference in resting pressure among patients without sepsis who had a J pouch (55 cmH$_2$O; 7–93 cmH$_2$O) compared with the W pouch (48 cmH$_2$O; 20–113 cmH$_2$O).

The median squeeze pressure following restorative proctocolectomy was 87 cmH$_2$O (25–180 cmH$_2$O), which was significantly less than that of the controls (143 cmH$_2$O (114–171 cmH$_2$O); $P<0{\cdot}01$). Of seven patients with a poor functional result, six had squeeze pressures which were less than the median value. The median maximum squeeze anal canal pressure in the seven patients with imperfect results was only 50 cmH$_2$O (35–107 cmH$_2$O) compared with 95 cmH$_2$O (25–180 cmH$_2$O) in the remainder ($P<0{\cdot}02$). The median maximal squeeze anal pressure in the eight patients who had pelvic sepsis was 67 cmH$_2$O (36–147 cmH$_2$O) compared with 87 cmH$_2$O (25–180 cmH$_2$O) in the remainder (not significant). Among those patients without pelvic sepsis there was no difference between the J pouch (87 cmH$_2$O; 25–140 cmH$_2$O) and the W pouch (93 cmH$_2$O; 50–180 cmH$_2$O):

Simultaneous measurement of ileal, pouch and anal pressures revealed that in most patients ileal and pouch pressures were lower than resting anal canal pressures (*Figure 2*). However, in three patients the resting ileal pressure was greater than the resting anal pressure and all three patients had episodes of anal incontinence. The median resting pouch pressure was 20 cmH$_2$O (7–86 cmH$_2$O) and the median ileal pressure was almost identical—22 cmH$_2$O (7–107 cmH$_2$O). Incremental increases of pressure in the pouch balloon were never associated with a recto-anal inhibitory response, whereas reflex relaxation of the anal sphincter in response to rectal distension was observed in all the controls. There was manometric evidence of increased small bowel contractility in response to pouch distension in eight patients, three of whom had pelvic sepsis.

Median pouch compliance was 6·8 ml/cmH$_2$O (2·1–17 ml/cmH$_2$O) compared with a median rectal compliance of 11·6 ml/cmH$_2$O (4·7–16·2 ml/cmH$_2$O) in controls ($P<0{\cdot}05$). Five of the seven patients with inferior functional results had a pouch compliance >10 ml/cmH$_2$O (*Figure 3*). The median compliance in eight patients with pelvic sepsis was 8·24 ml/cmH$_2$O (4·6–15·6 ml/cmH$_2$O) compared with 6·9 ml/cmH$_2$O (2·1–20·0 ml/cmH$_2$O) in those without sepsis (not significant) (*Figure 4*). The median compliance for the uncomplicated J pouch was only 4 3 ml/cmH$_2$O (2·1–15·6 ml/cmH$_2$O) compared with 10·0 ml/cmH$_2$O (7·1–20·0 ml/cmH$_2$O) for the W pouch ($P<0{\cdot}05$) (*Figure 5*). Threshold and constant volumes in the pouch patients did not differ significantly from rectal sensation in controls (*Figure 6*). Loss of sensation to electrical stimulation in the mid-zone of the anal canal was present in all except five of the pouch patients, being confined to those patients in this survey series in whom the anal transition zone had been deliberately preserved at operation (*Figure 7*).

Saline leaked much earlier in pouch patients during a 1 litre saline infusion (median, 320 ml; 60 ml–no leak), compared with

15 controls who had no leak from the rectum (median, no leak; 450 ml–no leak) (*Figure 8*). Similarly, median residual volumes were 550 ml in pouch patients (0–1000 ml) compared with a median value of 1 litre (350–1000 ml) in controls. With only one exception, all patients with disappointing results had an initial leakage volume of less than the median value (320 ml). Five of seven patients with a poor result had initial volumes of first leakage which were <150 ml.

In order to compare physiological abnormalities between groups, we scored the number of patients who had physiological measurements which lay outside the 95 per cent confidence limits (*Table 2*). One or more abnormal physiological parameters were present in 23 patients. The most frequent abnormality was the presence of low resting anal canal pressures. The number of abnormalities per patient in those who had an imperfect result was 4·28 compared with 1·26 in the remainder ($P<0{\cdot}02$). Similarly, sepsis was associated with a significantly

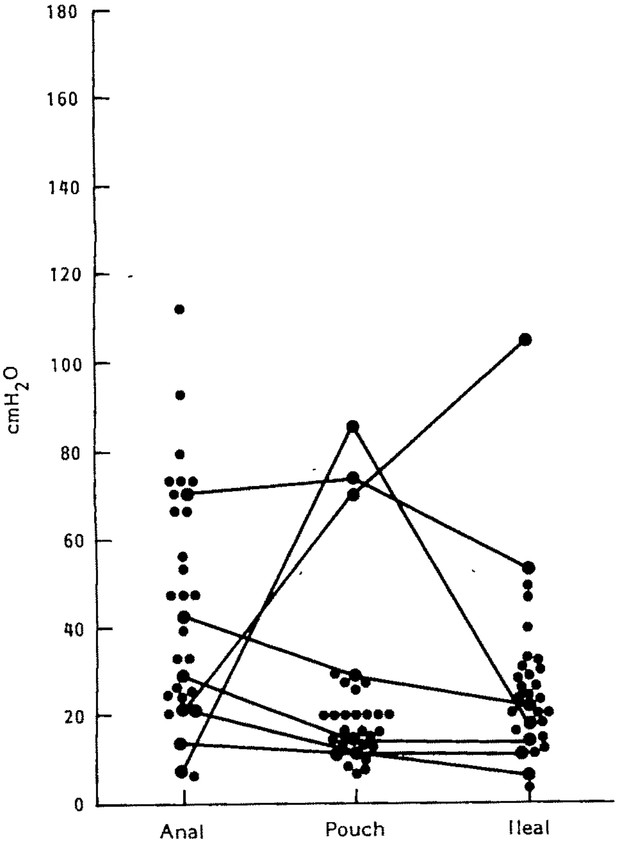


Figure 2 *Maximum resting anal, pouch and ileal pressures (cmH$_2$O) from simultaneous recordings after restorative proctocolectomy. Large filled circles denote patients with poor function*

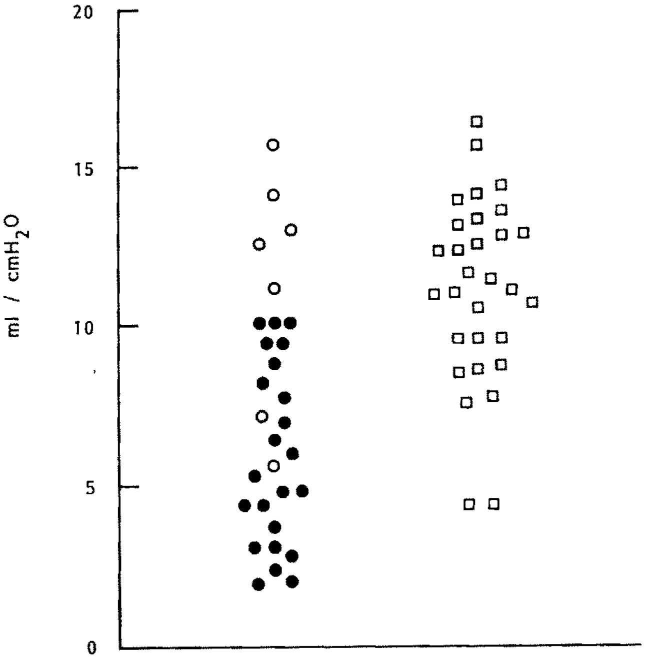


Figure 3 *Compliance (ml/cmH$_2$O) after restorative proctocolectomy compared with controls (P<0·05). ●, Patients with good function, ○, patients with poor function, □, controls*

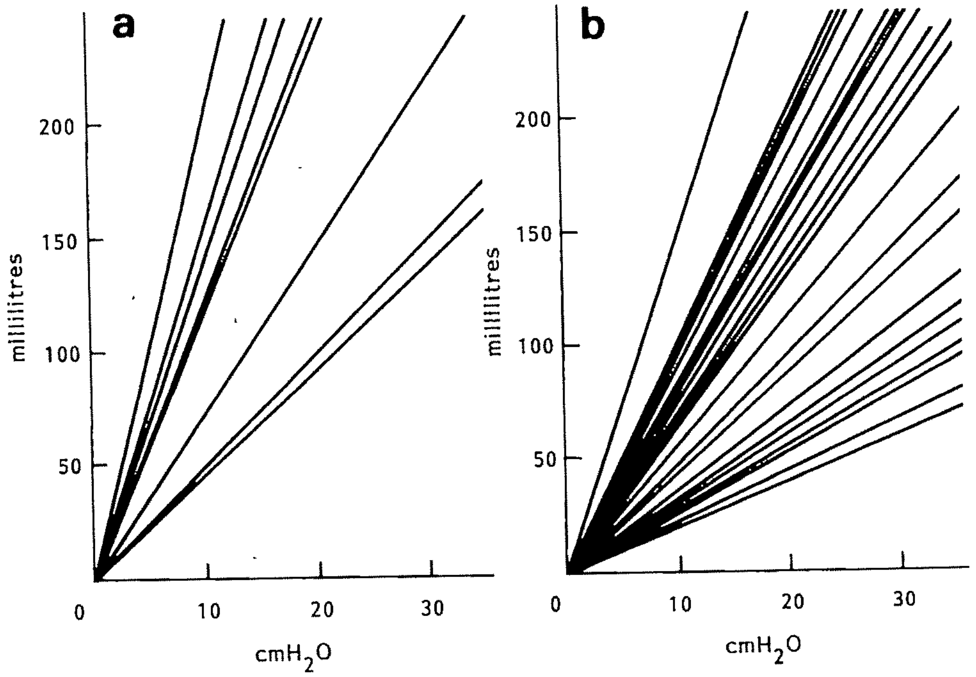


Figure 4 *Individual compliance results (ml/cmH$_2$O) after restorative proctocolectomy: a comparison of those* **a** *with pelvic sepsis (n=8) and* **b** *those without previous pelvic sepsis (n=22) (density points omitted for clarity) Differences not significant*

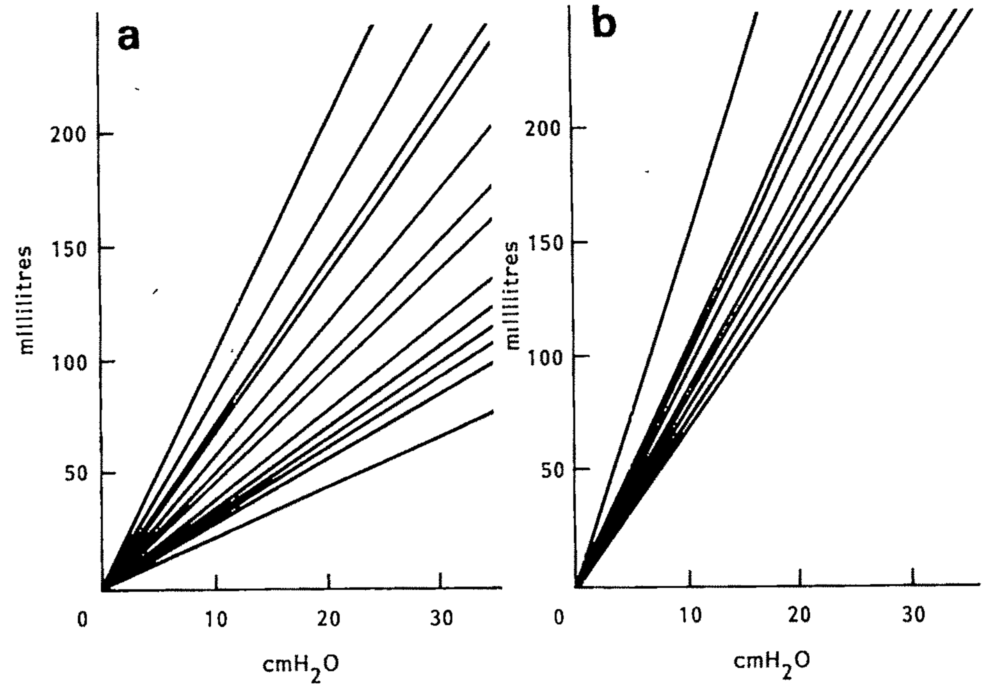


Figure 5 *Individual compliance results (ml/cmH$_2$O) in patients with no sepsis comparing* **a** *the J pouch* (n = *13;* $P < 0.05$) *with* **b** the W *pouch* (n = *9,* $P < 0.05$)

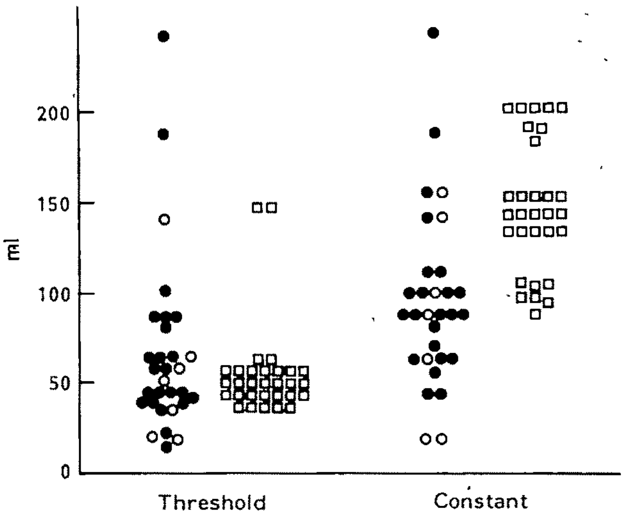


Figure 6 *Threshold and constant sensation (ml) compared in the pouch after restorative proctocolectomy and the rectum in controls.* ●, *Patients with good function,* ○, *patients with poor function;* □, *controls. Differences not significant*

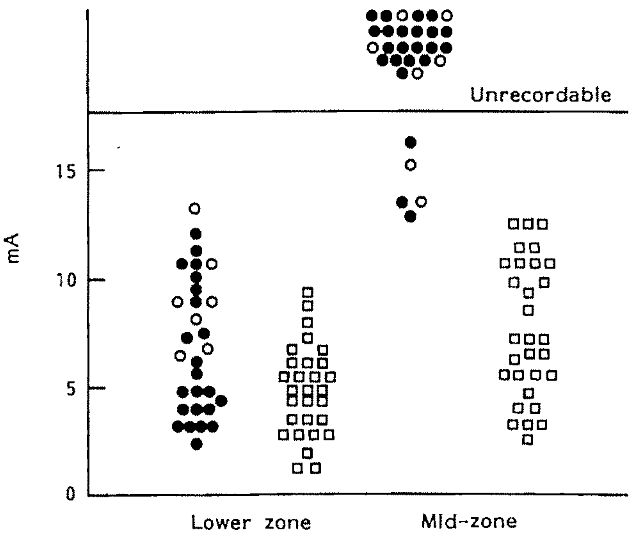


Figure 7 *Anal sensation (mA) in the midzone of the anal canal and after restorative proctocolectomy compared with controls* ($P<0.05$). ●, *Patients with good function;* ○, *patients with poor function;* □, *controls*

increased number of abnormalities per patient (sepsis, 3·75; no sepsis, 1·32; $P < 0.05$). By contrast, there was no significant difference in the number of abnormalities per patient when the J pouch (2·00) was compared with the W pouch (1·91).

The influence of duration of follow-up on pouch function was analysed among 13 patients who had had a J pouch and no postoperative sepsis. Four patients followed up for > 3 years had an average of 1·0 abnormalities per patient. Among five patients followed up between 1 and 3 years there were 1·2 abnormalities per patient compared with 1·8 among five patients followed up for > 1 year.

Discussion

The results of this physiological assessment of pouch anal function indicate that resting pressures are halved after restorative proctocolectomy compared with age- and sex-matched controls. Patients who had a less than satisfactory outcome had significantly lower resting anal canal pressures than the remainder. Low resting anal canal pressures appear to be independent of pouch design but associated with pelvic sepsis. These low resting anal pressures reflect impairment of internal anal sphincter function which is thought to be responsible for the increased incidence of soiling, especially at night time reported after restorative proctocolectomy[14–16]. Impaired internal anal sphincter function may be due to operative damage during anal mucosectomy[17] or to excessive anal retraction[6]. On the other hand, we were unable to demonstrate impaired anal function with the use of a Parks anal speculum for 20 min in constipated subjects[18]. Avoidance of anal mucosectomy may reduce the risk of damage to the internal anal sphincter[6] but excessive anal retraction is rarely necessary today for the small segment of anal mucosa that is removed during restorative proctocolectomy. It is possible, however, that retention of the entire anal transition zone and ileoanal anastomosis with the

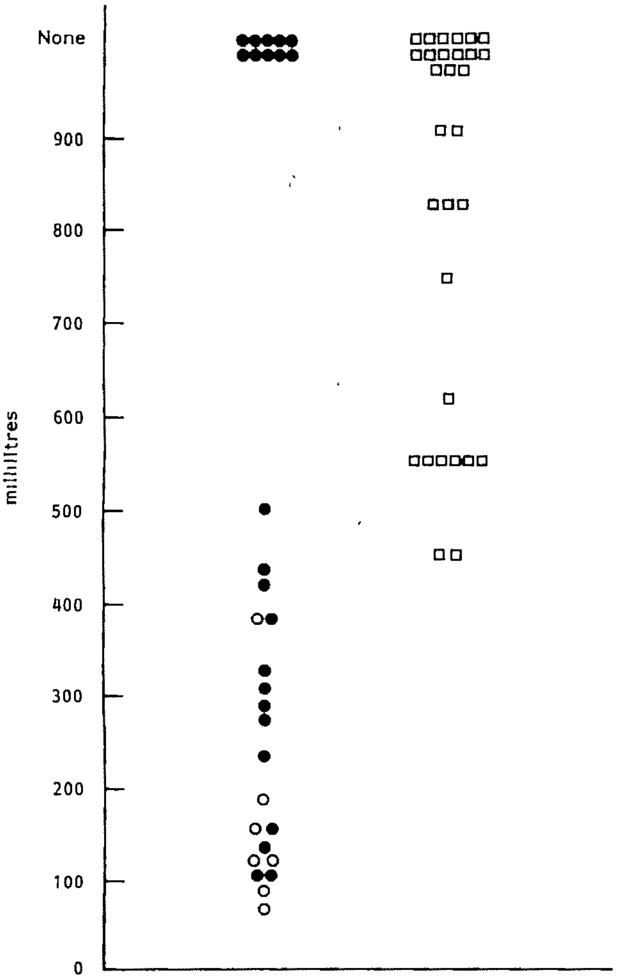


Figure 8 *Volume of first leak during saline infusion (ml) after restorative proctocolectomy compared with controls* ($P<0·05$) ●, *Patients with good function*, ○, *patients with poor function*; □, *controls*

Table 2 *Pouch patients abnormal results (outside 95% confidence limits)*

Measurement	Result	*n*
Resting anal pressure	<29 cmH_2O	11
Maximum squeeze pressure	<64 cmH_2O	8
Resting ileal pressure	>37 cmH_2O	5
Resting pouch pressure	>31 cmH_2O	3
Saline infusion		
First leak	<180 ml	9
Residual volume	<300 ml	7
Compliance	$>10·0$ ml/cmH_2O	7
Threshold pouch sensation	>100 ml	4

circular stapling device will further minimize operative damage to the visceral anal sphincter[19]. It is clear from these data, however, that damage to the internal anal sphincter is not solely a mechanical one but may also be seen in patients with severe pelvic sepsis

Squeeze anal canal pressures were also impaired compared with controls, and associated with poor results, but this was not a consequence of sepsis or pouch design. External anal sphincter function and puborectalis activity is almost certainly impaired because of some damage to the pelvic floor during the operation[20].

The three patients with high ileal and pouch pressures are interesting and may explain the occurrence of involuntary nocturnal leakage in some patients after this procedure. We believe that this phenomenon is associated with pelvic sepsis[21]. All of these patients had episodes of increased motor activity in the terminal ileum in response to pouch distension, a phenomenon which was also observed in five other patients with normal resting pouch and ileal pressures. Motor activity in the small bowel may be important in the pathogenesis of impaired functional results[22] and it is possible that this might be minimized by retention of the ileocaecal valve[23].

None of our patients had a normal recto-anal inhibitory reflex even though the anal transition zone had been preserved in five subjects. Retention of this sampling reflex[24] must be important for retaining normal defaecation and it is possible that preservation of the entire anal canal may preserve this reflex[19,25].

The pelvic pouch is less distensible than a normal rectum. Somewhat to our surprise, impaired compliance was not associated with a poor functional result. Furthermore, we found that sepsis had little influence on pouch compliance Like others, we confirm the pressure:volume advantage of the W pouch design over the J pouch[7,26].

Although anal sensation is impaired when the anal transition zone is excised, surprisingly pouch sensation does not differ from normal rectal sensation These afferent impulses must either arise from the pelvic floor or from stretch receptors in the bowel wall[27]

In view of the influence of operation on resting anal pressures, it is hardly surprising that early leakage of saline during the infusion test differs from that of normal subjects and was associated with poor results. As the irritability of the pouch is also being tested, we were not surprised to find that early leakage of saline was often observed in patients with pelvic sepsis. We are not aware of any other reports using the saline infusion test on pouch patients.

The number of physiological abnormalities was found to be significantly increased in patients with a functional score of 3 or more and correlated closely with the incidence of pelvic sepsis. The number of abnormalities was independent of pouch design and there was only a small reduction with duration of follow-up. We acknowledge that so far we have no data on pouch emptying, bacterial overgrowth, small bowel transit or morphological changes in the pouch. However, these data clearly imply that operative damage to the internal anal sphincter and irritability of the small bowel associated with pelvic sepsis are factors of great importance in the functional outcome of restorative proctocolectomy.

References

1 Becker JM, Hillard AE, Mann FA, Kestenberg A, Nelson JA Functional assessment after colectomy, mucosal proctectomy and endorectal ileoanal pull-through. *World J Surg* 1985,9 598–605
2. Nasmyth DG, Johnston D, Godwin PGR, Dixon MF, Smith A, Williams NS. Factors influencing bowel function after ileal pouch–anal anastomosis. *Br J Surg* 1986, **73**: 469–73.
3. Taylor BM, Beart RW Jr, Dozois RR, Kelly KA, Wolfe BG, Ilstrup DM. The endorectal ileal pouch–anal anastomosis current clinical results. *Dis Colon Rectum* 1984; **27**· 347–50
4 Suzuki H, Fujioka M. Rectal pressure and rectal compliance *Jpn J Surg* 1982, **12**: 79–81.
5 Fiorentini MT, Locatelli L, Ceccopieri B *et al.* Physiology of ileoanal anastomosis with ileal reservoir for ulcerative colitis and adenomatosis coli. *Dis Colon Rectum* 1987; **30** 267–72
6 Keighley MRB Abdominal mucosectomy reduces the incidence of soiling and sphincter damage after restorative proctocolectomy and J pouch *Dis Colon Rectum* 1987; **30**: 386–90
7 Dozois RR, Goldberg SM, Rothenberger DA, Utsunomiya J, Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis. a comparison of three reservoir designs *Br J Surg* 1985, **72**· 470–4
8 Stryker SJ, Borody TJ, Phillips SF, Kelly KA, Dozois RR, Beart RW Jr Motility of the small intestine after proctocolectomy and ileal pouch–anal anastomosis. *Ann Surg* 1985, **201**. 351–6.
9 O'Connell PR, Rankin DR, Weiland LH, Kelly KA Enteric bacteriology, absorption, morphology and emptying after ileal pouch–anal anastomosis *Br J Surg* 1986, **73**. 909–14
10. Keighley MRB, Winslet MC, Yoshioka K, Lightwood R Discrimination is not impaired by excision of the anal transition

zone after restorative proctocolectomy. *Br J Surg* 1987; **84**: 1118–21.

11. Primrose JN, Holdsworth PJ, Nasmyth DG, Womack N, Neal DE, Johnston DE. Intact anal sphincter with end-to-end ileo-anal anastomosis for ulcerative colitis: comparison with mucosal proctectomy and pull-through anastomosis. *Br J Surg* 1987; **74**: 539.
12. Yoshioka K, Kmiot W, Keighley MRB. Factors influencing motor function after restorative proctocolectomy. *Gut* 1988, in press.
13. Farthing MJG, Lennard-Jones JE. Sensibility of the rectum to distension and the anorectal distension reflex in ulcerative colitis. *Gut* 1978; **19**: 64–9.
14. Nicholls RJ Restorative proctocolectomy with various types of reservoir. *World J Surg* 1987; **11**: 751–62.
15. McHugh SM, Diamant NE, McLeod R, Cohen Z. S-Pouches vs J-Pouches A comparison of functional outcomes. *Dis Colon Rectum* 1987; **30**· 671–7
16. Pemberton JH, Kelly KA, Beart RW Jr, Dozois RR, Wolfe BG, Ilstrup DM. Ileal pouch–anal anastomosis for chronic ulcerative colitis. Long-term results *Ann Surg* 1987; **206**: 504–9.
17. Sharp FR, Bell GA, Seal AM, Atkinson KG. Investigations of the anal sphincter before and after restorative proctocolectomy *Am J Surg* 1987, **153**: 469–72
18. Yoshioka K, Keighley MRB. Randomised trial comparing anorectal myectomy and controlled anal dilation for outlet obstruction. *Br J Surg* 1987; **74**. 1125–9.
19. Heald RJ, Allen DR Stapled ileo-anal anastomosis· a technique to avoid mucosal proctectomy in the ileal pouch operation. *Br J Surg* 1986; **73**: 571–2.
20. Harms BA, Hamilton JW, Yamamoto DT, Starling JR. Quadruple-loop (W) ileal pouch reconstruction after proctocolectomy: analysis and functional results. *Surgery* 1987; **102**. 561–7
21. Winslet MC, Flinn R, Keighley MRB. Factors influencing the outcome of restorative proctocolectomy *Gut* 1987; **28**: A1365–6
22. O'Connell PR, Pemberton JH, Kelly KA. Motor function of the ileal J pouch and its relation to clinical outcome after ileal pouch–anal anastomosis *World J Surg* 1987; **11**: 735–41.
23. Johnston D, Holdsworth PJ, Nasmyth DG *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. *Br J Surg* 1987; **74**: 940–4.
24. Grant D, Cohen Z, McHugh S, McLeod R, Stern H Restorative proctocolectomy. Clinical results and manometric findings with long and short rectal cuffs. *Dis Colon Rectum* 1986; **29**: 27–32.
25. Lane RHS, Parks AG. Function of the anal sphincter following colo-anal anastomosis. *Br J Surg* 1977; **64**· 596.
26. Nicholls RJ, Pezim ME Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72**: 470–4.
27. Beart RW Jr, Dozois RR, Wolff BG, Pemberton JH Mechanisms of rectal continence. Lessons from the ileoanal procedure. *Am J Surg* 1985; **149**· 31–4.

Br. J. Surg. 1988, Vol. 75, October,
1003–1007

Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique

The anal canal in health is extremely sensitive to thermal stimuli. If temperature sensation plays a part in sensory discrimination two conditions must be fulfilled: there must be a temperature gradient along the anorectum and rectal contents must be able to come into contact with the sensitive anal mucosa. In a study of 53 normal subjects we demonstrated this temperature gradient with a median temperature difference between the rectum and lower, mid and upper anal canal of 0·4, 0·2 and 0·1°C respectively. The second condition was examined in 15 normal ambulatory subjects by measuring mid-anal sphincter (SP) and rectal pressures (RP) with a microtransducer catheter. The signals were digitalized and recorded in a portable electronic memory for later computer display, and analysis. Marked spontaneous sphincter relaxation resulting in equalization of RP and SP occurred 7 times per hour (1–4). The conscious sensation of the presence of flatus was associated with an SP reduction of 30 mmHg (20–50 mmHg) and an RP increase of 7 mmHg (0–15 mmHg), such that RP ≥ SP in 80 per cent of 144 recorded events. Using this new technique we have demonstrated the highly dynamic nature of the anal sphincter. Several times an hour the sphincter relaxes with subsequent equalization of rectal and anal pressures, allowing entry of rectal contents into the anal canal so that its presence and nature can be determined.

Keywords: Ambulatory, anorectal physiology, anal sensation

R. Miller, G. T. Lewis*, D. C. C. Bartolo, F. Cervero† and N. J. McC. Mortensen‡

*Department of Surgery and *Department of Medical Physics, Bristol Royal Infirmary and †Department of Physiology, University of Bristol, Bristol, UK*

Correspondence to:
Mr R. Miller, Royal United Hospital,
Combe Park, Bath, Avon, UK

Our current understanding of anorectal physiology in health and disease has been derived from studies of patients in 'laboratory' conditions over relatively short periods of time. Routine manometric and many radiological investigations are performed with the patient lying still in the left lateral position[1–3]. Although these studies have provided much essential information their application is limited because of the unnatural surroundings and immobility of the patient.

The object of this study was to investigate anal sphincter activity in conditions as near normal as possible. In particular we wished to elucidate the mechanism by which the presence and nature of rectal contents were recognized by normal subjects. We have previously demonstrated that the anal canal in health is extremely sensitive to temperature[4]. If this is involved in the perception of rectal contents two further conditions must be met: (1) there must be a temperature difference between the anal canal mucosa and rectal contents; (2) rectal contents have to be able to come into contact with the sensitive anal mucosa. Both these conditions are examined in this study. In addition, the manometric changes that accompanied the passing of flatus were noted.

Patients and methods

Patients

Anal canal temperature measurements were taken from 53 subjects, 30 male and 23 female, median age 64 years (range 21–90 years). These patients had been admitted for surgery unrelated to the colon or rectum and had no alimentary complaints.

Ambulatory recordings were made in a separate group of 15 patients, 10 male, 5 female, median age 52 years (range 29–80 years). Thirteen had no anorectal complaints and were awaiting surgery for some condition unrelated to the alimentary tract; the remaining two patients were taken from the colonoscopy follow-up list after right-sided colonic polypectomy at least 6 months before the investigation and a normal colonoscopy within 2 weeks of the test. No bowel preparation was used and investigations were performed in the mid-afternoon.

Methods

Measurement of anorectal temperature. A thermocouple was built by the Department of Physiology in Bristol University specifically to measure temperature in the anorectum. It was designed to avoid error due to heat conduction down the shaft of a normal mercury thermometer and to enable very accurate recordings from discrete areas of the anorectum to be made. It consisted of a nickel–aluminium/nickel–chromium thermocouple set on the surface of a small plastic dome 4 mm in length and diameter, and fitted on to the end of a PVC catheter, 3 mm in diameter (*Figure 1*). This was connected to the digital thermometer (Type 2501, Comark Ltd, Littlehampton, UK). The temperature in the anorectum was measured in the lower, mid and upper zones of the anal canal and from the mid-rectum (0·5, 1·5, 2·5 and 10 cm from the anal verge respectively). Repeat measurements were taken from 10 patients to assess reproducibility.

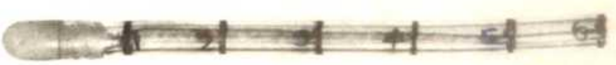


Figure 1 *Photograph of the thermocouple used to measure anal temperature*

---

‡ *Present address: John Radcliffe Hospital, Headington, Oxford, UK*

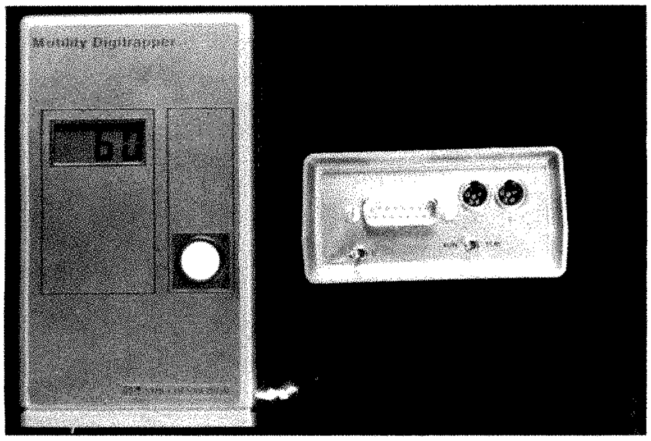


Figure 2 *The 'Digitrapper' box*

Table 1 *Temperatures recorded from different levels in the anorectum*

Level	Temperature (°C)
Anal canal	
Lower	36·87 (35·9–37·8)
Middle	37·10 (36·3–38·1)
Upper	37·25 (36·5–38·2)
Rectum	37·30 (36·7–38·3)

Values are medians with ranges in parentheses

Ambulatory anorectal manometry. A soft, flexible microtransducer catheter, 2 mm in diameter was used in order to minimize the disturbance to the anorectum (16C/Sil 3, Gaeltec Ltd, Isle of Skye, UK). It carried three pressure-sensitive microtransducers, one at the tip and one each 4 cm and 6 cm proximally. It was connected to a portable box of electronics (Motility Digitrapper, Synectics Medical Inc., Stockholm, Sweden) which was originally designed to measure oesophageal motility and was adapted for use in the anorectum. It allowed 3 h recordings from two pressure channels to be stored in a digital memory. This was the maximum time of recording permitted by the memory capacity of the box. The pressure from either channel could be visualized on a liquid crystal display and it also had an event marker button so that subjects could denote on the trace of pressure change any event which they felt (*Figure 2*). It was found in preliminary investigations that the recording of pressures using this system was subject to a degree of drift and that this could be minimized by allowing a 30 min period to 'warm up' the system, after which the memory was cleared. It was calibrated using a pressurized chamber connected to a mercury manometer and zeroed at atmospheric pressure. A station pull-through of the anal sphincter was performed (taking into account radial variation)[5] and the catheter was placed so that the transducers faced laterally: the lower transducer recorded mid-anal canal pressure and rectal pressure was recorded by the transducer at the tip. The digitrapper box permitted only two-channel recording and therefore the middle transducer on the catheter was not used. The catheter was then strapped to the natal cleft with adhesive tape up to the anal verge. The digitrapper was positioned at the subject's waist on a belt and he or she was familiarized with the event marker. The subjects were instructed to press the marker once when the presence of flatus was felt and twice when it was felt to pass *per anum*. Two subjects were asked to contract the anal sphincter when they felt the sensation of flatus for the last half hour of the recording, the aim being to determine whether the falls in pressure could be explained by displacement of the catheter such that the lower transducer was in the rectum and therefore not recording sphincteric activity.

Preliminary investigations using this technique revealed a very characteristic trace when subjects walked and these sections were excluded from the analysis to reduce possible error due to catheter displacement. In addition, in one subject the artefact induced by movement of the catheter in the anal canal was observed.

The subjects were permitted to do what they wished over the 3 h period and on completion the information was offloaded on to a computer (Type 1512, Amstrad, Brentwood, Essex, UK) which, with the appropriate software (Motiligram, Synectics, Sweden), allowed the traces of pressure change to be displayed and assisted with the analysis of results.

Statistical analysis

All intergroup comparisons were analysed using the Mann–Whitney *U* test. Reproducibility of temperature measurement was determined by the Spearman ranked correlation coefficient.

Results

Anorectal temperature measurements

The median temperature differences between the rectum and lower, middle and upper anal canal were 0·4, 0·2 and 0·1°C respectively. These results indicate that a temperature gradient exists in the anorectum, with a progressive reduction of temperature from rectum to lower anal canal. The results of actual temperatures recorded are presented in *Table 1*. Reproducibility of temperature measurements in the lower, middle and upper anal canal and rectum were: r_s 0·86, 0·94, 0·92 and 0·97 respectively ($P<0·001$).

Ambulatory anorectal manometry

The median duration of the studies was 2·8 h. Normal slow waves were seen in a few patients and ultraslow wave activity was also occasionally seen.

The most striking feature of the traces of pressure change were numerous falls in sphincter pressure to such an extent that it was equal to or less than rectal pressure (*Figure 3*). This occurred 7 times per hour (range 1–41 times), of which 60 per cent were not felt by the subjects. There were, in addition to these, numerous other falls in sphincter pressure that did not result in equalization with rectal pressure (*Figure 4*).

Awareness of the presence of flatus was noted, in all, 144 times during the total of 40 h recording with a median frequency of 3/h (range 1–7/h). It was associated with a fall in sphincter pressure of 30 mmHg (20–50 mmHg) and a rise in rectal pressure of only 7 mmHg (0–15 mmHg). Sphincter pressure was equal to or lower than rectal pressure in 80 per cent of cases. A typical example of the pressure changes associated with the sensation of flatus is shown in *Figure 5*. Only 6 per cent of sensations were not associated with a fall in sphincter pressure. Prolonged reductions of the sphincter pressure were observed in 12 of the 15 subjects such that rectal and mid-anal sphincter pressures were the same for up to 3 minutes at a time (*Figure 6*). These occurred at a median frequency of 1 per 3-hour period (0–12/h) and lasted for 60 s (20–180 s). The episodes were often associated with the awareness of flatus being present just before the pressure began to rise to its 'resting' level.

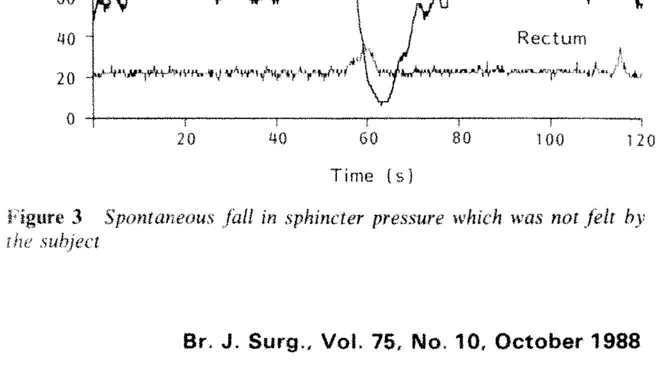


Figure 3 *Spontaneous fall in sphincter pressure which was not felt by the subject*

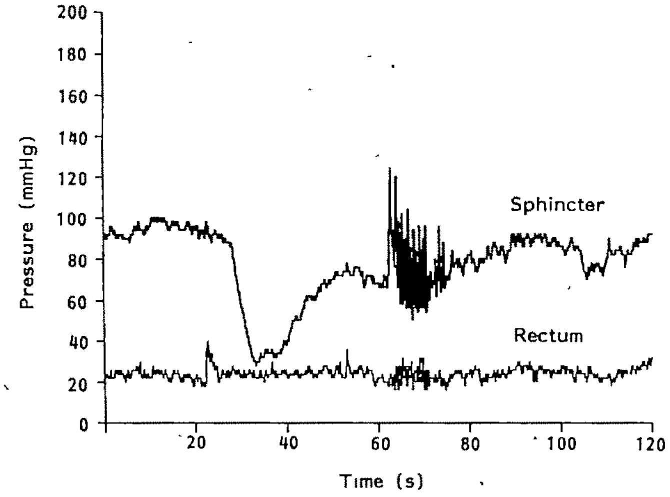


Figure 4 *Sphincteric relaxation which did not result in equalization with rectal pressure. These were very frequent events. This is followed by an example of the artefact induced by moving the catheter in the anal canal, which bears no resemblance to the more prolonged falls in pressure associated with the sensation of flatus*

During both the transient reductions and the more prolonged events, normal maximum voluntary squeeze contractions were seen in the patients requested to 'squeeze' the sphincter, indicating that the catheter was still in the anal sphincter and had not been displaced into the rectum or to the exterior (*Figure 7*).

The manometric changes that occurred when flatus was passed consisted of a reduction of sphincter pressure by 35 mmHg (0–88 mmHg) with a relatively small rise in rectal pressure of 8 mmHg (range −10 to 88 mmHg). Fifty-four of these events were recorded, the median frequency being one per hour (range 0–3·5/h). Neither the rise in rectal pressure nor the fall in sphincter pressure that occurred on passing flatus were statistically different from those that occurred when flatus was simply felt to be present.

In two subjects a more pronounced rise in rectal pressure occurred when flatus was passed but this always accompanied a marked fall in sphincter pressure (*Figure 8*).

In one subject the rectum filled during the course of the study, which permitted the effect on sphincter activity to be observed. In the first hour with an empty rectum he behaved in very much the same way as 'normal' with frequent relaxations of the sphincter. As the rectum filled, the pressure recorded by the rectal microtransducer gradually increased because of direct

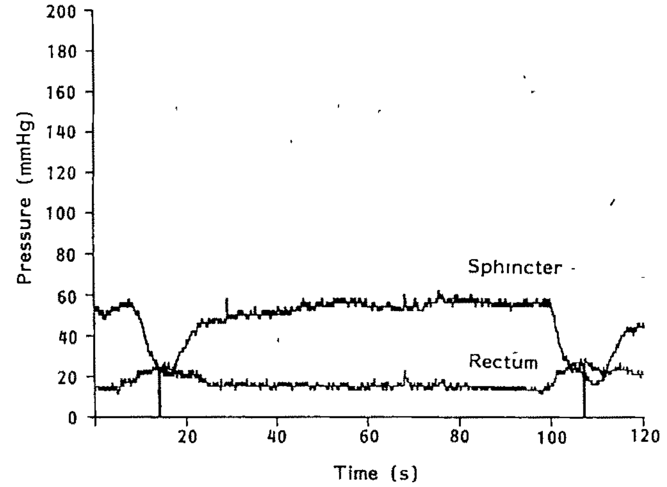


Figure 5 *Manometric changes associated with the sensation of the presence of flatus (denoted by the vertical lines at 15 and 108 s). The principal change is a fall in sphincter pressure so that rectal and anal pressures equalize*

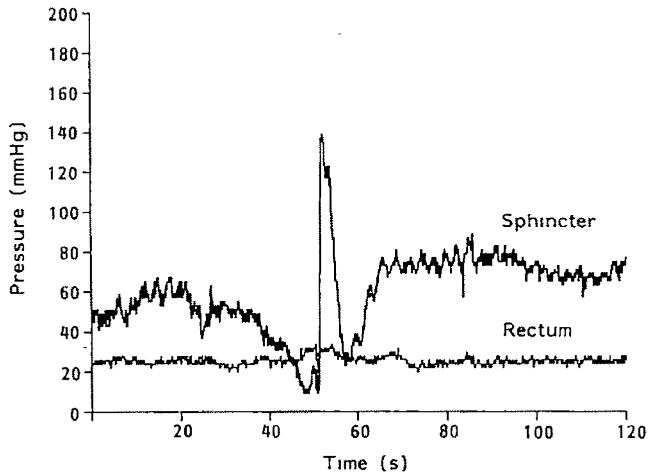


Figure 7 *In this example the subject was requested to squeeze the sphincter on the sensation of flatus. The external sphincter contraction was recorded as a rise in pressure indicating that the microtransducer was still in the anal canal*

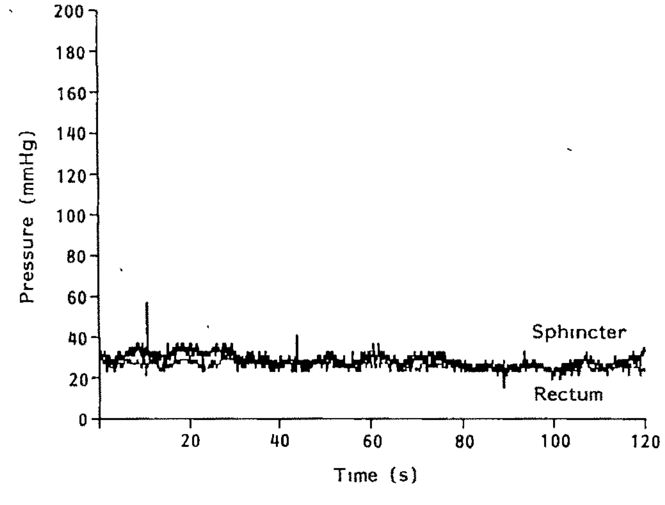


Figure 6 *An example of more prolonged sphincteric relaxation such that mid-anal and rectal pressures were equal for 2 min*

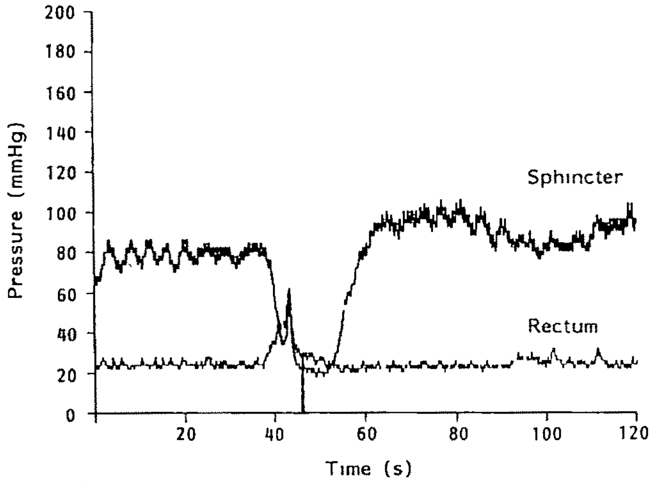


Figure 8 *Anorectal manometry on passing flatus. The principal change was a fall in sphincter pressure and in this example the rectal pressure also increased considerably*

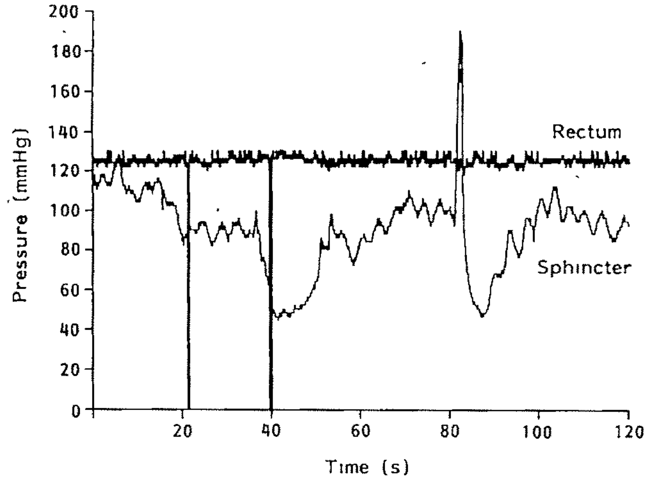


Figure 9 *Manometric changes on feeling and then passing flatus with a full rectum (denoted by the vertical lines at 22 and 40 s respectively). The sphincter relaxed to allow flatus to enter the anal canal but after this event there was a marked rise in sphincter pressure, characteristic of an external sphincter contraction*

pressure of stool on the transducer membrane. The most interesting change occurred in the sphincter pressure after flatus was either felt or passed. After these events there was a marked rise in sphincter pressure, characteristic of an external sphincter contraction (*Figure 9*).

Five patients ate sandwiches during the course of the recordings but this produced no obvious change in anorectal manometry. Similarly, the effect of micturition was recorded on several occasions and high anal canal pressures were seen at the end of urination but too few patients were studied for any conclusions to be drawn.

Discussion

An essential prerequisite to the study of physiological disorders is a thorough understanding of the normal mechanisms governing the system under investigation. Our current concepts of the physiology of continence are for the most part based on static measurements of patients in the left lateral position. Some workers have attempted to introduce more dynamic assessments[6–8] but even these studies are limited in their application. They are performed in unfamiliar and often intimidating surroundings in their effort to simulate stresses on the continence mechanism or defaecation.

This study represents an attempt to observe 'normal' sphincter activity in subjects largely free from these constraints, and has demonstrated frequent sphincteric relaxation allowing the possibility of contact between the rectal contents and sensitive anal mucosa. Temperature sensation is important for sensory discrimination and it is probable that the difference in temperature between stool in the rectum and the anal canal would contribute to sensory discrimination of rectal contents. It is suggested that this would result in the central nervous system being continually updated with information regarding the presence and nature of rectal contents. This may reach consciousness on occasions but how often this occurs is likely to be very variable and to depend on the activities and distractions of the individual.

Some caution is necessary in extrapolating conclusions regarding the movement of gut contents from manometric data. Movement of flatus into the anal canal has not been demonstrated in this study. There is, however, a high probability that this does occur, bearing in mind the proximity of the two pressure sensors, the ease of movement of gaseous contents and the fact that flatus was often felt on equalization of rectal and anal pressures a few seconds before it was passed, when its presence in the anal canal was beyond doubt.

The total range of frequency at which equalization of rectal and sphincter pressures occurred was considerable (1–41/h). This is likely to be a reflection of the volume of flatus and stool contents entering the rectum and therefore largely dependent on diet[9]. The effect of diet was observed when one subject was studied while on his normal diet and again after 24 hours taking free fluids only. On his normal diet the hourly frequency of equalization of anorectal pressure, sensation and passing of flatus was 4·6, 2·5 and 1·4 respectively. On a free fluid diet equalization occurred only twice in the 3 h period and flatus was neither felt nor passed.

While rectal distension is known to cause internal sphincter relaxation[10], distension of the gut by solid and gaseous contents some distance from the lower rectum may have an effect on internal sphincter activity. Naudy and co-workers found diminishing sensitivity to the threshold distension that induced internal sphincter relaxation as the distending balloon was moved more proximally from rectum to sigmoid colon[11]. They also noted marked internal sphincter relaxation during propulsive activity in the lower sigmoid and upper rectum. Similarly, Browning and Parks observed that propulsive colonic activity induced by the topical application of bisacodyl caused internal sphincter relaxation and proposed the reflex was mediated via the myenteric plexus[12]. It would seem probable, therefore, that many of the falls in sphincter pressure recorded in this study were due to contraction or distension of the sigmoid colon and upper rectum. Internal sphincter relaxation induced by colonic activity may explain why 60 per cent of the recorded sampling episodes were not associated with the subjective awareness of rectal contents being present. If the rectum was empty, sphincteric relaxation induced by such activity would not result in stimulation of the anal mucosa.

The correlation of manometric changes with the awareness of rectal contents provides considerable support for the concept of anorectal 'sampling' proposed by Duthie and Bennett[13] although it does not elucidate which receptors are responsible. We have previously demonstrated that the anal mucosa is highly sensitive to thermal stimuli[4] but it is possible that sphincter relaxation is perceived because of changes in stretch receptor activity in the muscles rather than any effect of mucosal stimulation by the rectal contents. It is difficult, however, to conceive how these receptors would be able to differentiate between relaxation induced by solid or gaseous rectal contents. Furthermore, the relaxation induced by the recto-anal inhibitory reflex does not result in any sensation of flatus and in fact is hardly ever perceived by the subject under study. In addition to thermal stimulation, mechanical stimulation of the anal mucosa and rectal stretch receptors are likely to be essential in enabling rectal contents to be perceived.

Our results also shed some light on other aspects of sphincteric activity, and differ from findings in 'laboratory' conditions. Flatus was observed to pass as the sphincter relaxed so that its pressure equalized with rectal pressure, which rose only slightly compared with the drop in sphincter pressure. In one-third of these events there was no accompanying rise in rectal pressure at all. In contrast, Finlay and co-workers reported in nine subjects that the mechanism by which flatus was continently expelled was by forcing it through a tightly closed sphincter and concluded that 'inappropriate puborectalis spasm noted in the solitary rectal ulcer syndrome represents the normal mechanism of passing flatus'[14].

The rectum filled in one subject during the course of the recording period and sphincteric activity changed considerably. The sphincter was seen to contract after flatus was either felt or passed and this may represent contraction of the sphincter to push back stool that had entered the anal canal when it had relaxed in response to flatus. If this is the case, it helps to explain how the sphincter works to maintain continence in the presence of a full rectum; further studies are in progress to investigate the finding.

In conclusion, this study has shown that anorectal sampling occurs in normal ambulatory patients and is associated with the conscious awareness of flatus. In conjunction with the thermal gradient in the anorectum and the sensitivity of the anal canal, this supports the concept of the sensitive anal mucosa being essential for sensory appreciation of rectal contents.

Acknowledgements

Mr Miller is supported by a grant from the Medical Research Council.

References

1. Read MG, Read NW, Haynes WG, Donnelly TC, Johnson AG. A prospective study of the effects of haemorrhoidectomy on sphincter function and anal continence. *Br J Surg* 1982; **69**. 396–8.
2. Dickinson VA. Maintenance of anal continence: a review of pelvic floor physiology *Gut* 1978, **19**: 1163–74.
3. Bartolo DCC, Roe AM, Locke-Edmunds JC, Virjee J, Mortensen NJMcC. Flap valve theory of anorectal incontinence. *Br J Surg* 1986; **73**: 1012–14.
4. Miller R, Bartolo DCC, Cervero F, Mortensen NJMcC. Anorectal temperature sensation: a comparison of normal and incontinent patients. *Br J Surg* 1987; **74**: 511–15.
5. Miller R, Bartolo DCC, Roe AM, Mortensen NJMcC. Assessment of microtransducers in anorectal manometry. *Br J Surg* 1988; **75**. 40–3.
6. Read NW, Haynes WG, Bartolo DCC, Hall J, Read MG. Donnelly TC, Johnson AG. Use of anorectal manometry during rectal infusion of saline to investigate sphincter function in incontinent patients. *Gastroenterology* 1983; **85**· 105–13
7. Bartolo DCC, Read MG, Read NW The saline continence test. Dynamic studies in faecal incontinence, haemorrhoids and the descending perineum syndrome. *Acta Gastroenterol Belg* 1985, **48**: 39–50.
8. Womack NR, Williams NS, Holfield JHM, Morrison JFB, Simpkins KC. New method for dynamic assessment of anorectal function in constipation. *Br J Surg* 1985; **72**: 994–8
9. Read NW. Gastrointestinal gas. In: Jewell DP, Gibson PR, eds. *Topics in Gastroenterology*. Oxford Blackwell Scientific, 1985 283–8.
10. Gowers WR. The autonomic action of the sphincter ani. *Proc R Soc Lond* 1887; **26**. 77–84
11. Naudy B, Planche D, Monges B, Salucci J. Relaxations of the internal anal sphincter elicited by rectal and extrarectal distensions in man. In· Roman C, ed *Gastrointestinal Motility*. Lancaster. MTP Press. 1983 451–8.
12. Browning GGP, Parks AG. Effect of colonic motor activity on the internal anal sphincter. *Gut* 1982, **23**· A914
13. Duthie HL, Bennett RC. The relation of sensation in the anal canal to the functional anal sphincter. a possible factor in anal continence. *Gut* 1963; **4**: 179–82.
14. Finlay IG, Carter K, McLeod I. A comparison of intra-rectal infusion of gas and mass on anorectal angle and anal canal pressure. *Br J Surg* 1986; **73**: 1025A.

Br. J. Surg. 1988, Vol. 75, October,
1008–1011

Prospective randomized trial to compare the stapled double lumen pouch and the sutured quadruple pouch for restorative proctocolectomy

M. R. B. Keighley, K. Yoshioka and W. Kmiot

Department of Surgery, The General Hospital, Steelhouse Lane, Birmingham, B4 6NH, UK

Correspondence to:
Professor M. R. B. Keighley

Thirty-three consecutive patients having restorative proctocolectomy since April 1986 were randomly allocated to reconstruction using a stapled J pouch ($n = 18$) *or a sutured W pouch* ($n = 15$). *There were no deaths, but one patient required pouch excision for ischaemia (J). One patient developed a leak from the pouch necessitating loop ileostomy (J) and one patient had a low pouch vaginal fistula successfully treated by a seton (W). There were no other major complications. Median (range) operative time was 200 min (165–290) for J pouch and 255 min (220–330) for the W pouch* ($P < 0{\cdot}05$). *In 24 patients followed up for more than 4 months after restoring intestinal continuity, median frequency of defaecation over 24 h was 4 (3–6) for the J pouch and 4 (3–6) for the W pouch. There was no incontinence, urgency or soiling. These results indicate that the quicker J pouch provides identical functional results to the larger W pouch in this series of patients.*

Keywords: Restorative proctocolectomy, ileoanal pouch, J pouch and W pouch

Restorative proctocolectomy has become an accepted operation in selected patients for ablating colorectal disease while retaining continence[1–3]. The operation has been used principally for ulcerative colitis and familial adenomatous polyposis[4–6]. The original straight ileoanal anastomosis fell into disrepute because of severe diarrhoea[7,8]. The triplicated pouch popularized by Parks *et al.*[9] was initially associated with a need to catheterize the pouch in a high proportion of patients because of poor emptying associated with a long efferent limb. The double lumen J pouch was popularized by Utsunomiya *et al.*[10] for patients with polyposis coli. The J pouch has been used extensively in North America for patients with ulcerative colitis; however, frequency of defaecation tends to be high[11]. For this reason, Pezim and Nicholls popularized the quadruple W pouch on the basis that capacity and compliance were greater than with other pouch designs[12]. Furthermore, sequential studies at St. Mark's Hospital (London, UK) indicated that frequency after the use of the W pouch was significantly lower than with all other pouch designs[13], presumably owing to the special geometric configuration of this model[14].

We believe that there are many factors other than pouch design that influence frequency of defaecation. A multivariate analysis of patients operated on in this unit has identified the importance of the 'learning curve', method of mucosectomy, length of rectal cuff and pelvic sepsis on outcome[15]. In order to negate the influence of the learning curve phenomenon on functional outcome, we decided to undertake a prospective randomized trial to compare the stapled double lumen J pouch with the sutured quadruple lumen W pouch. Variables included diagnosis, previous colectomy and the use of a covering ileostomy. Nevertheless, total rectal excision and abdominal mucosectomy to the level of the dentate line (anal transition zone excised) and sutured intra-anal ileoanal anastomosis were performed in all patients. To minimize the influence of the learning curve phenomenon, entry to the trial was only commenced after the surgeon had undertaken 25 operations. The author (M.R.B.K.) had constructed eight W pouches and fourteen J pouches before starting the trial.

Patients and methods

All patients having a restorative proctocolectomy and ileo–pouch–anal anastomosis operated on at the General Hospital, Birmingham by one surgeon since April, 1986 were entered into the trial. Analysis of outcome was undertaken in February 1988 by an independent observer (W.K.) who was unaware of the type of pouch construction. During these 22 months, 33 patients underwent restorative proctocolectomy. Eighteen patients were randomized by hospital registration number, to the double lumen J pouch (median age 30 years. range 14–62; 11 males) and 15 to the quadruple W pouch (median age, 34 years; range 17–47; 8 males). Although most patients had ulcerative colitis ($n = 25$) there were two patients who, despite pre-operative colonoscopic biopsy evidence of ulcerative colitis, had Crohn's disease in the colectomy specimen. Three patients had familial adenomatous polyposis and there were three more patients who developed a megarectum after previous subtotal colectomy and ileorectal anastomosis for chronic constipation and megacolon (*Table 1*) Eighteen patients had had a previous colectomy for acute fulminating colitis or for chronic constipation. Although 21 of the patients had a proximal loop ileostomy, there were 12 who had no covering ileostomy. Despite these variables all patients in the trial had a total rectal excision and abdominal mucosectomy[16]. Furthermore, in all these patients the entire anal transition zone was excised and the pouch–anal anastomosis was sutured as an intra-anal procedure using a Parks' retractor[17].

The double lumen J pouch was constructed after closing the terminal ileum with a TA 30® or by continuous suture. Two 20-cm limbs of

Table 1 *Patient related variables in the two pouch groups*

Variables	J pouch ($n = 18$)	W pouch ($n = 15$)
Diagnosis		
Ulcerative colitis	14	11
Crohn's disease	1	1
Familial adenomatous polyposis	2	1
Megarectum	1	2
Previous colectomy	8	10
No covering ileostomy	6	6

Table 2 *Complications*

	J pouch ($n = 18$)	W pouch ($n = 15$)
Wound sepsis	2	3
Pelvic sepsis	2	1
Leak from pouch	1	—
Stricture	1	3
Pouch vaginal fistula	—	1
Intestinal obstruction	3	—
Pouch ischaemia	1*	—
Pouchitis	2	2

* Pouch removed

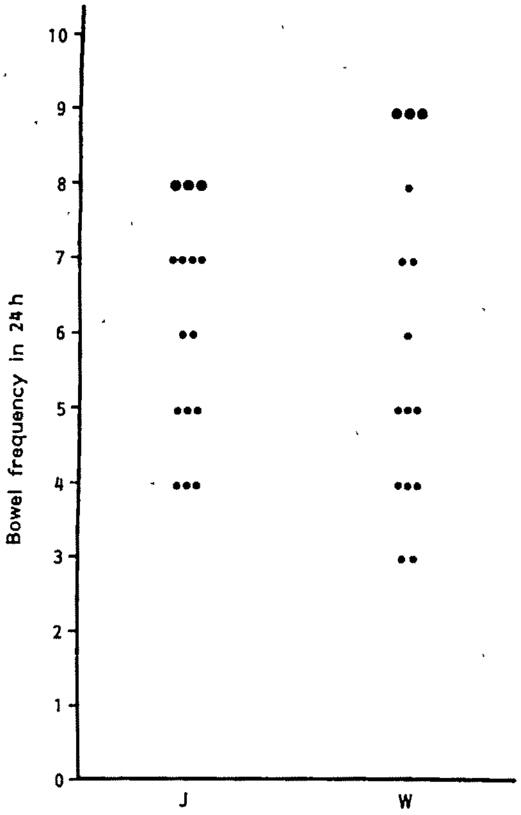


Figure 1 *The frequency of bowel action per 24 h comparison of the J and the W pouch. Large filled circles: follow-up <4 months*

terminal ileum were used and the pouch was stapled using the GIA® or PCL 50® introduced through an enterotomy in the apex of the ileal loop. The quadruple limb W pouch was sutured using a continuous extra-mucosal 30 Maxon® suture after prior closure of the terminal ileum. The W pouch was constructed using four 10-cm lengths of terminal ileum. At the completion of pouch construction, the pouch was inflated with saline to test for leaks; the median maximum operative pouch capacity was 190 ml (160–240) for the J pouch and 230 ml (200–260) for the W pouch.

Before pouch construction attention was given to ensuring that the apex of the pouch would reach the anal verge without tension. Consequently, the origin of the superior mesenteric vessels was dissected from the undersurface of the pancreas and the origin of the divided middle colic vessels was freed from the parent vessels The duodenum and the duodenojejunal flexure were also completely mobilized. Usually the ileocolic vessels required division and in some patients the superior mesenteric artery had to be divided distal to a large branch provided that there was an adequate peripheral arcade in the small bowel mesentery[18]. The ileoanal anastomosis was performed using an intra-anal retractor using interrupted 20 Vicryl® sutures on a 20 mm round-bodied needle lubricated with liquid paraffin. All sutures were placed and the retractor removed before they were tied.

Results

There were no postoperative deaths. One patient (J pouch) has had to have her pouch removed because of ischaemia (*Table 2*). This was in a patient where the superior mesenteric artery had been divided. Unfortunately the trephine in the abdominal wall for the proximal loop ileostomy was too tight and the entire small bowel distal to the covering ileostomy became ischaemic and had to be resected. One other diabetic patient (J pouch) developed pelvic sepsis after closure of the loop ileostomy. At relaparotomy a leak was demonstrated by air insufflation of the pouch under water and, after repair, a loop ileostomy was re-established. The ileostomy has now been closed and the functional results are satisfactory.

Wound sepsis was recorded in five patients (15 per cent). Including the leak from the pouch, pelvic sepsis occurred in three patients (9 per cent). Four patients developed transient strictures at the ileoanal anastomosis; all were managed by gentle dilatation, usually without anaesthesia. One patient developed a low fistula from the site of the ileoanal anastomosis to the vulva. This was managed by repeated tightening of a Prolene® seton. Although there is a persistent short stricture, the patient has complete continence and there is no soiling. Three patients had an episode of intestinal obstruction, two of whom required laparotomy because this failed to resolve with conservative management. Four patients had pouchitis during follow-up which responded promptly to metronidazole therapy; three of these patients had an ileoanal stricture at the time of pouchitis. The incidence of complications did not differ between the groups.

The median total operating time was 200 min (165–290) for the stapled J pouch compared with 255 min (220–330) for the sutured W pouch ($P < 0.05$).

Functional results could not be evaluated in three patients at the time of assessment (all J pouches) because of pouch excision for ischaemia, secondary loop ileostomy for pouch leak (both described) and a third patient who requested a secondary loop ileostomy because of diarrhoea (median frequency per 24 h: 7). One of these patients has subsequently had the stoma closed. The median frequency of defaecation in the 30 evaluable patients was identical (*Figure 1*; *Table 3*). No patient is incontinent and only four patients have urgency, but these four have only been followed up for <4 months. Two patients followed for >4 months complained of occasional nocturnal soiling (one J and one W pouch). One patient followed for >4 months occasionally wears a pad at night-time for fear of occasional leakage (J pouch). All patients claim they can discriminate passage of gas from semi-solid or liquid stool.

Analysis of the 24 patients, who have been followed up for >4 months after restoring intestinal continuity, reveals no difference between the groups, the median frequency being four per day and once at night in both groups. Only seven of twelve patients having a J pouch and five of twelve with a W pouch needed to continue taking antidiarrhoeal drugs.

Table 3 *Functional results in evaluable patients*

	J pouch ($n = 15$)*	W pouch ($n = 15$)
Frequency: day	5 (3–7)	5 (3–8)
night	1 (0–1)	1 (0–2)
antidiarrhoeals	10	8
Incontinence	0	0
Urgency	2†	2†
Soiling: day	0	0
night	1	1
Pads: day	0	0
night	1	0
Failure of discrimination	0	0

* 3 patients could not be evaluated at assessment; † patients followed up for <4 months. Values in parentheses are ranges

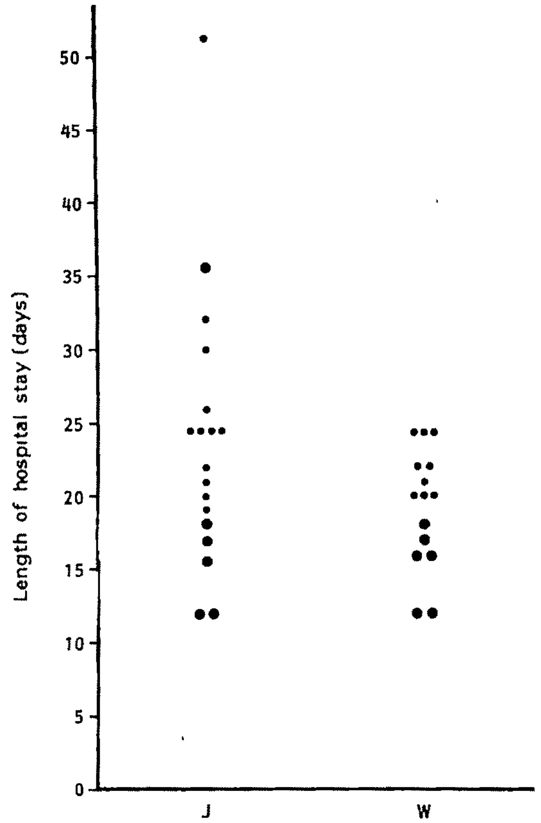


Figure 2 *The length of hospital stay in days after the two pouch procedures. Large filled circles: no covering ileostomy*

Duration of hospital stay was similar and the impact of avoiding an ileostomy on hospital stay is shown in *Figure 2*.

Discussion

Despite small numbers this randomized trial has failed to show any significant advantage of the potentially more capacious W pouch over the more rapidly constructed stapled J pouch. This series consists of a consecutive group of 33 patients under the care of one surgeon who had already gained experience of the procedure and each design of pouch from 25 earlier operations. Hence, this comparison is quite different from those reported from other UK centres[19,20] where functional results of the larger pouch have been shown to be superior. In the St. Mark's series, the W pouch was introduced after the three-lumen S pouch because of dissatisfaction with the functional results. The four-lumen pouch was introduced only after considerable experience of the operation had been gained, whereas the smaller S and J pouches were used much earlier in the series where there was a higher incidence of pelvic sepsis. Indeed, another surgeon in the same institution has reported good results with the long J pouch (P. R. Hawley, personal communication). For this reason, we felt compelled to compare these two pouch designs by a randomized trial.

The incidence of pelvic sepsis falls with increasing experience of the operation[13,21,22]. We believe that pelvic sepsis is one of the factors which has the greatest impact on functional outcome[15]. Indeed, in a recent physiological assessment we have shown that pelvic sepsis is a much more important determinant of pouch function than pouch design[23]. Pelvic sepsis is associated with a stiff non-compliant pouch, an irritable small bowel and low anal pressures[24,25]. For these reasons we believe that comparison of pouch design must be undertaken after a surgeon has worked his way through the learning curve attending this operation.

We accept that some patients have had a previous colectomy, but an audit from this unit has failed to demonstrate any detrimental effect of previous colectomy on outcome[15]. Although the study was not confined to patients with ulcerative colitis, the incidence of familial adenomatous polyposis and functional bowel disorders was evenly distributed between the groups. Other variables such as the extent of rectal and anal mucosectomy were standardized as was the method of ileoanal anastomosis.

The duration of operation was significantly shorter using the stapled J pouch. The impact of stapling over suture techniques for construction of the J pouch was not tested and it is likely that the use of the stapler was largely responsible for the operation time difference between the groups. Admittedly avoidance of a loop ileostomy shortened the duration of the operation and the duration of hospital stay but the numbers having no covering stoma were identical in both groups. As in the experience of others[26], elimination of a proximal ileostomy in this series had no detrimental influence on complications or functional outcome. Indeed, it is our usual practice to dispense with a loop ileostomy, particularly as we now use a stapled ileoanal anastomosis[27]. A further advantage of the stapled pouch and ileoanal anastomosis is that the entire operation (even with a colectomy) can be completed in between 2 and 2½ h.

We see no obligation to increase the number of patients entered into this study as no advantage has been demonstrated with the use of the more prolonged operation. Indeed, in contrast to Thomson *et al.*'s theory[14] we believe that the longer more oval J pouch fits more comfortably in the narrow male pelvis than the rounder and shorter quadruple pouch.

Appendix

The manufacturers of the registered products mention in the text are as follows: TA 30® and GIA®, Autosuture Company, Conneticut, USA; PCL 50® Prolene® and Vicryl®, Ethicon Ltd., Edinburgh, UK; 30 Maxon®, Davis and Geck, Gosport, UK

References

1. Fasth S, Oresland T, Ahren C, Hulten L. Mucosal proctectomy and ileostomy as an alternative to conventional proctectomy. *Dis Colon Rectum* 1985; **28**: 31–4
2. Cohen Z, McLeod RS, Stern H, Grant D, Nordgren S. The pelvic pouch and ileoanal anastomosis procedure. Surgical technique and initial results. *Am J Surg* 1985, **150**. 601–7.
3. Rothenberger DA, Buls JG, Nivatvongs S, Goldberg SH. The Parks' S ileal pouch and anal anastomosis after colectomy and mucosal proctectomy *Am J Surg* 1985; **149**: 390–4.
4. Williams NS, Johnston D. The current status of mucosal proctectomy and ileo-anal anastomosis in the surgical treatment of ulcerative colitis and adenomatous polyposis. *Br J Surg* 1985, **72**. 159–68.
5. Fonkalsrud EW Endorectal ileal pullthrough with isoperistaltic reservoir for colitis and polyposis. *Ann Surg* 1985; **202**: 145–52.
6 Schoetz DJ, Coller JA, Veidenheimer MC Ileoanal reservoir for ulcerative colitis and familial polyposis. *Arch Surg* 1986; **121**: 404–9.
7. Telander RL, Perrault J Colectomy with rectal mucosectomy and ileoanal anastomosis in young patients. Its use for ulcerative colitis and familial polyposis. *Arch Surg* 1981; **116**: 623–9.
8. Taylor BM, Beart RW Jr, Dozois RR, Kelly KA, Phillips SF Straight ileoanal anastomosis versus ileal pouch–anal anastomosis after colectomy and mucosal proctectomy. *Arch Surg* 1983; **118**: 696–701
9. Parks AG, Nicholls RJ, Belliveau P. Proctocolectomy with ileal reservoir and anal anastomosis. *Br J Surg* 1980; **67** 533–8.
10. Utsunomiya J, Iwama T, Imajo M *et al.* Total colectomy, mucosal proctectomy, and ileoanal anastomosis. *Dis Colon Rectum* 1980; **23**: 459–66.
11. Metcalf AH, Dozois RR, Kelly KA, Beart RW Jr, Wolff BG. Ileal 'J' pouch–anal anastomosis. Clinical outcome. *Ann Surg* 1985; **202**: 735–9.
12. Pezim ME, Nicholls RJ. Quality of life after restorative proctocolectomy with pelvic ileal reservoir. *Br J Surg* 1985; **72**: 31–3.

13. Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72**: 470–4.
14. Thomson WHF, Simpson AHRW, Wheeler JL. Mathematical prediction of ileal pouch capacity. *Br J Surg* 1987; **74**. 567–8.
15. Winslet MC, Flinn R, Keighley MRB. Factors influencing the outcome of restorative proctocolectomy. *Gut* 1987; **28**: A1365–6.
16. Keighley MRB. Abdominal mucosectomy reduces the incidence of soiling and sphincter damage after restorative proctocolectomy and J pouch. *Dis Colon Rectum* 1987; **30**: 386–90.
17. Keighley MRB, Winset MC, Pringle W, Allan RN. The pouch as an alternative to permanent ileostomy. *Br J Hosp Med* 1987; **4**: 286–94.
18. Smith L, Friend WG, Medwell SJ. The superior mesenteric artery. The critical factor in the pouch pull-through procedure. *Dis Colon Rectum* 1984; **27**: 741–4.
19. Nasmyth DG, Williams NS, Johnston D. Comparison of the function of triplicated and duplicated pelvic ileal reservoirs after mucosal proctectomy and ileo-anal anastomosis for ulcerative colitis and adenomatous polyposis. *Br J Surg* 1986; **73**: 361–6.
20. Nicholls RJ, Roskowitz RL, Shepherd NA. Restorative proctocolectomy with ileal reservoir. *Br J Surg* 1985; **72**: S76–9.
21. Taylor BM, Beart RW Jr, Dozois RR, Kelly KA, Wolfe BG, Ilstrup DM. The endorectal ileal pouch–anal anastomosis: current clinical results *Dis Colon Rectum* 1984; **27**: 347–50
22. Nasmyth DG, Johnston D, Godwin PGR, Dixon MF, Smith A, Williams NS. Factors influencing bowel function after ileal pouch–anal anastomosis. *Br J Surg* 1986; **73**: 469–73
23. Keighley MRB, Yoshioka K, Kmiot W, Heyen F. Physiological parameters influencing function in restorative proctocolectomy and ileo–pouch–anal anastomosis. *Br J Surg* 1988; **75**: 997–1002.
24. Schraut WH, Rosemurgy AS, Wang C-H. Determinant of optimal results after ileoanal anastomosis anal proximity and motility patterns of the ileal reservoir. *World J Surg* 1983; **7** 400–8.
25. Becker JM, Hillard AE, Mann FA, Kestenberg A, Nelson JA Functional assessment after colectomy, mucosal proctectomy, and endorectal ileoanal pull-through. *World J Surg* 1985; **9**. 598–605.
26. Metcalf AM, Dozois RR, Kelly KA, Wolff BG. Ileal pouch–anal anastomosis without temporary, diverting ileostomy. *Dis Colon Rectum* 1986; **29**: 33–5.
27. Heald RJ, Allen DH. Stapled ileo-anal anastomosis: a technique to avoid mucosal proctectomy in the ileal pouch operation. *Br J Surg* 1986; **73**: 571–2.

Br. J. Surg. 1988, Vol. 75, October, 1012–1015

Abdominoperineal and anterior resection of the rectum with retrocolic omentoplasty and no drainage

S. R. G. Smith, I. Swift, H. Gompertz and W. N. W. Baker

Department of Surgery, Ashford Hospital, Ashford, Middlesex, UK

Correspondence to:
Mr S. R. G. Smith, Selly Oak Hospital, Birmingham, UK

Forty consecutive patients scheduled for either low anterior resection or abdominoperineal resection of the rectum have been studied. After standard procedures, carried out by all grades of surgeons, the omentum was mobilized as a pedicle graft based on the left gastro-epiploic arcade and transposed to the pelvis or perineum. All wounds were closed primarily without drainage. Twenty-six patients had anterior resection, 11 abdominoperineal resection and 3 an extended Hartmann's operation. Patients were assessed clinically and radiographically by Gastrografin® enema and ultrasound for evidence of anastomotic leakage, pelvic collections and wound healing. After anterior resection there were three radiological leaks and no overt clinical leaks. One patient had a collection related to a leak. Of 11 perineal wounds 8 healed primarily in 2 weeks and all healed by 4 weeks. There was no frank wound breakdown. The three patients who had Hartmann's operations all healed without complication. There were no unavoidable complications of the procedure. Retrocolic omentoplasty is a simple, safe and effective adjunct to rectal surgery. The additional time taken (15–20 min) is well rewarded by sound healing of these operations.

Keywords: Omentum, anterior resection, rectal anastomosis, abdominoperineal, perineal wounds

The incidence of leakage at rectal anastomoses varies considerably, between 0·5 per cent and 30 per cent, and accounts for a substantial morbidity, mortality and prolonged hospital stay[1]. After anterior resection drainage of the pelvis is common practice in Britain. Eighty-five per cent of surgeons routinely drain the operation[2] with the objective of evacuating the retrorectal space of blood and serosanguinous exudate. Experimentally it has been shown that the pelvic dead space contributes to leakage[3] but it is questionable whether drainage is the optimum method of resolving the problem. Several experimental studies have questioned the role of surgical drains in causing leakage[4,5] particularly when they are placed next to an anastomosis[6]. In the pelvis the drain unavoidably lies near or adjacent to the anastomosis, perhaps increasing rather than reducing the risk of dehiscence.

It has long been recognized that the omentum can protect anastomoses and secure healing[7–9] but this potential has not been widely exploited. In this report we describe our experience of using the omentum for low colorectal anastomoses and primary perineal wound closure after abdominoperineal excision of the rectum. The technique employed was modified from that previously described in 1977 by Goldsmith[10] and more recently by Bunt *et al.*[11] in 1984.

Patients and methods

Since 1 March 1986 all patients scheduled for anterior resection or abdominoperineal (A–P) rectal excision under the care of one consultant surgeon (W.N.W.B.) have been entered prospectively into the study. Patients underwent the standard surgical practice of the firm, which for restorative resections included bowel preparation with Picolax and antibiotic prophylaxis with cefuroxime 1·5 g and metronidazole 500 mg IV on induction of anaesthesia and 8 hourly cefuroxime 750 mg and metronidazole 500 mg IV for 24 h. For abdominoperineal resections a rectal washout only was administered. All operations were carried out under general anaesthesia supplemented by epidural Marcain for A–P resections.

Technique of retrocolic omentoplasty

A standard resection and anastomosis or synchronous abdominoperineal excision was performed. Anastomoses were constructed using one layer of interrupted 2/0 Nurolon*. The omentum was divided longitudinally towards the transverse colon and the left half mobilized from the transverse colon. When mobilization of the splenic flexure was required the omentum was freed simultaneously. In most cases additional length of omentum was required and this was achieved by separating the omentum from the greater curve of the stomach, while preserving the gastro-epiploic artery on the omental side. The omentum was then brought down, usually through the lesser sac and transverse mesocolon to lie in the para-aortic gutter, or laterally when the colon had been extensively mobilized. The omentum was dropped over the pelvic brim and placed behind and to the right of the bowel, filling the space. Initially the anastomosis was circumferentially wrapped but this was abandoned after two patients developed strictures.

After perineal dissection the omentum was placed so as to fill the pelvic cavity and floor. The pelvic peritoneum was sutured to the omentum with a running 2/0 chromic catgut suture and the perineal subcutaneous fat and skin sutured over the omentum to achieve primary closure. All wounds were closed without drainage. The right half of the omentum was used to protect the bowel deep to the abdominal incision which was closed in layers with monofilament nylon.

Postoperatively patients were given clear fluids orally on the return of bowel sounds or passage of flatus per rectum and a light diet was started after the passage of stool. Patients with a perineal wound were nursed in standard hospital beds with regular two-hourly turning followed, on the second postoperative day, by sitting out on chairs with foam cushions. Ring cushions were not used.

Assessment

Patients were observed clinically on routine rounds and four-hourly oral temperature was recorded until it was no more than 37°C for 24 h. The number of days of temperature elevation above 37·5°C was recorded.

Between the 10th and 14th postoperative day patients underwent an ultrasound scan of the pelvis to look for fluid collections. After anterior resection, between the 10th and 14th postoperative day, a Gastrografin

---

* *Nurolon is a trademark of Ethicon Ltd, UK.*

0007-1323/88/101012-04$3 00

Table 1 *Details of patients and operations*

	Diagnosis			Sex		
	Cancer	Diverticular disease	Colitis	Male	Female	Total
Anterior resection	19	6	1	9	17	26
Hartmann's operation	3	—	—	2	1	3
A–P resection	9	—	2	8	3	11
Total	31	6	3	19	21	40

Table 2 *Grade of surgeon performing operations*

	Consultant	Senior registrar	Registrar	Total
Anterior resection	9	11	6	26
Hartmann's operation	1	2	—	3
A–P resection	10	1	—	11
Total	20	14	6	40

enema was performed The anastomosis was further assessed by sigmoidoscopy at the first out-patient follow up, usually at 6 weeks, to check for defects or strictures and measure its height (cm) from the anal margin. Sigmoidoscopy was repeated at 3 months.

After perineal dissection primary healing was defined as complete by the day of suture removal. At 3 months the perineal wounds were assessed for strength by asking the patient to strain down while leaning towards the examination couch.

Patients

Retrocolic omentoplasty was used in 40 consecutive patients with a mean age 65±10·9 years The diagnoses, sex and operations performed are shown in *Table 1* and the grade of surgeon in *Table 2*.

Bowel preparation before anastomosis was described as good (clean, dry/mucous colon) in 20 patients and fair (mild faecal remnants) in 2 patients. Four patients, two of whom had emergency procedures for obstruction, were poorly prepared and underwent on-table antegrade colonic washout[12] before primary anastomosis. Five patients, who all had anterior resection, had additional *en bloc* resections which included hysterectomy (2), a cuff of bladder (2), loops of small bowel (2) or vaginal vault (1) Other incidental findings included a carcinoid tumour of the appendix and a lymphoma.

Sites of anastomoses

The anastomosis was in the lower third of rectum in 9 patients (defined as up to 7·5 cm from the anal margin), in the middle third in 10 (between 7 5 and 12 cm) and in the upper third in 7 (above 12 cm). The upper third anastomoses were included when, at the time of operation, the mesorectum was mobilized and the anastomosis was constructed below the highest, posterior, reflection of the peritoneum

Results

One patient, a woman aged 82, died from myocardial infarction on the ninth postoperative day. Post-mortem examination confirmed that the anastomosis was intact and that there was no evidence of a pelvic collection. One patient with Parkinson's disease suffered a myocardial infarction which, combined with his immobility, delayed his discharge after A–P resection to 33 days.

Within 30 days of operation there were four overt abdominal wound infections (10 per cent), one burst abdomen and no perineal sepsis. One patient had bleeding through the perineal wound which was traced to the cut edge of the omentum where diathermy coagulation had been used. The patient made an uneventful recovery although primary healing was delayed to 4 weeks by a few granulations in the perineum where a drain had been inserted during re-exploration.

There were no instances of early (within 30 days) or late small bowel obstruction and none of the patients required reoperation for omental ischaemia. The mean pre- and postoperative haematological and biochemical results and the days of postoperative temperature and stay in hospital are shown in *Table 3*. The surgical results are shown in *Table 4*.

Anterior resection

One patient developed signs on the sixth postoperative day suggestive of anastomotic leakage. Lower abdominal pain and fever for 24 h settled on treatment with clear fluids and antibiotics. Later the Gastrografin enema confirmed the presence of a leak and ultrasound showed a small retrorectal collection. This patient had a very scanty omentum which only covered the pelvic brim. He later developed a soft anastomotic stricture, which was easily dilated digitally. In two patients a delayed rise in temperature was explained by proven urinary tract infection, with an appropriate response to treatment. None of the patients showed any clinical evidence of intraperitoneal or pelvic collections.

All patients who survived had a Gastrografin enema and in three a radiological leak was demonstrated. Two patients were entirely asymptomatic but one, a 29-year-old woman with carcinoma and an anastomosis at 7 cm, after 10 days at home had a vaginal discharge which lasted 4 days. This was thought to be due to a small collection. She had not had an ultrasound examination.

Ultrasound examinations were attempted in 21 patients but only 17 were technically satisfactory. Only the patient with a leak was found to have a collection.

During out-patient follow-up a total of four anastomotic strictures were found. One was dilated digitally and one, in the 29-year-old woman, was dilated with a sigmoidoscope at 6 weeks. The other two required dilatation under general anaesthetic twice and three times respectively after resections for diverticular disease and carcinoma. Gastrografin studies were normal in both cases.

Abdominoperineal resection

Nine patients had a traditional perineal dissection for carcinoma using an elliptical para-anal incision with preservation of the coccyx. Two patients with ulcerative colitis had an intersphincteric dissection for non-emergency proctocolectomy. Both were receiving steroid therapy at the time of operation. Apart from the patient who bled, all achieved primary healing. Perineal sutures were removed on average on the 12th day (12·5±3·4, range 10–16 days). Longer stays in hospital were not caused by problems related to the wounds

Ultrasound examinations were done in eight patients and in five were satisfactory. None demonstrated an intrapelvic collection.

All the perineal wounds have remained soundly healed with no evidence of prolapse but the average follow-up is only 9·4±5·8 months (range 2–21). One patient re-presented 3 months after A–P resection with a large deep perineal abscess from which *Escherichia coli* was isolated. Postoperatively he had required prolonged bladder drainage by indwelling catheter and at 2 months had an endoscopic incision of a posterior urethral stricture. The abscess may have been due to this procedure. His ultrasound examination at 10 days had shown no evidence of a collection.

Table 3 *Pre-operative biochemical and haematological values and postoperative temperature and days in hospital*

	Haemoglobin† (g/dl)	Total protein† (g/l)	Days of fever‡	Postoperative days in hospital‡
Anterior resection	13·8±1·7	74·6±4·5	1·0 (0–2)	11 (7–26)
Hartmann's operation	12·1±1·3	73·3±1·2	1, 2, 2*	16, 14, 14*
A–P resection	13·2±1·5	71·0±4·4	1·0 (0–7)	14 (8–33)

* Actual values; † mean ± s.d.; ‡ median and range; A–P, abdominoperineal

Table 4 *Results of rectal surgery with omentoplasty in 40 patients*

	Clinical	Radiological
Anterior resection		
Leaks	1	3/25
Collections	0	1/17
Strictures	4	
Hartmann's operation		
Collections	0	0/3
Primary heal	3	
A–P resections		
Collections	0	0/8
Primary heal		
2 weeks	8	
4 weeks	11	

Hartmann's operation

Three patients with advanced carcinoma were treated by an extended Hartmann's procedure to avoid the perineal dissection. Tube drains were not used and the omentum was placed down to the rectal stump, which was oversewn in one case. All of these patients healed *per primam*, with no collections.

Discussion

Previous reports have proclaimed the benefit to healing of using the omentum to fill the pelvic space after urological and rectal surgery[8–10,13–16] and also after oesophageal anastomosis[17]. The value to rectal anastomosis has not been evaluated critically by objective tests, such as contrast enema, but two previous reports of unspecified numbers of patients have claimed no leakage[10,13].

Of our 26 patients undergoing anterior resection, all but the patient who died had a Gastrografin enema. Three (12 per cent) of these examinations demonstrated a leak. None of the patients had clear-cut clinical evidence of a leak although one suffered lower abdominal pain and fever for 24 h which, with the knowledge of the enema, was attributable to a leak. As adequate omentum was not available it can be argued that this case should not be regarded as a failure of the technique. In the case of the 29-year-old woman, the leak was entirely asymptomatic, although she later developed a vaginal discharge. This would not normally be regarded as a significant clinical leak. In the third case the leak was asymptomatic.

After low anterior resection overt clinical leakage rates of 4 per cent, 8 per cent and 10 per cent have been attributed, in uncontrolled series, to various forms of surgical drainage of the presacral space[18–20]. Although there is substantial experimental evidence[4–6] that drains are harmful to colonic healing this hypothesis has not been tested clinically. Matheson *et al.*[21], who recently reported only 3 clinical leaks in 140 single-layer colorectal anastomoses, stated that the anastomoses were never drained but a fine suction drain was placed into the sacral hollow. In their series among the 41 anastomoses constructed below 12 cm there were only 2 (5 per cent) leaks. Without monitoring by contrast enema we would have claimed a zero leakage rate with omentoplasty in the present series.

Experimentally in dogs[3] a large dead space, achieved by wide pelvic clearance and colorectal anastomosis, has been associated with increased anastomotic leakage rates. When pedicled omentum was used to fill the pelvis, healing was much improved even in the presence of blood inoculated with *E. coli.* The ability of omentum to clear infection has also been demonstrated after deliberate soiling of aortic grafts[22].

Various techniques involving some form of drainage have been advocated for the management of perineal wounds after rectal excision. One of the more successful methods involved a complex suction irrigation system and achieved 90 per cent primary healing at 3 weeks and all wounds healed by 2 months[23,24]. In contrast, primary closure of the perineum and pelvic floor with suction drainage of the dead space will achieve healing in two-thirds of patients by 3 months[25–27] with some 20 per cent remaining unhealed by 6 months. With open drainage and packing as few as one-third have healed by 3 months[25,27].

With an omental pedicle graft, primary healing of the perineal wound has been achieved in more than 90 per cent of patients by 2 months[14–16]. In two of these reports[15,16] drains were used in addition to omentum. In the largest series[14] 38 out of 49 healed primarily and 48 were healed at a mean of 40 days. In our experience the omentum alone has worked satisfactorily, and primary healing was achieved in eight of the eleven cases within 12 days. Of those with delayed healing, one followed secondary insertion of a drain while the other two patients had intersphincteric dissections with prolonged bloody discharge but primary healing was complete by 3 and 4 weeks. Thus all patients were healed within 4 weeks. In one case of tumour the rectum was perforated with considerable contamination. The wound was irrigated with cetrimide and closed. Antibiotics were administered for 5 days and primary healing occurred without complication.

The extended Hartmann's operation has a reputation for postoperative pelvic sepsis[28,29] although, in modern practice, this may be undeserved[30]. We undertook this procedure three times and Moreaux *et al.*[14] reported use of the omentum without drainage in 12 cases, also with no septic complications.

The technique takes only 15–20 min to perform and we had only one complication, namely haemorrhage from the cut edge of the omentum. Diathermy coagulation had been used instead of ligation, as discussed by others[9]. The dominant blood supply to the omentum comes from the right gastro-epiploic arcade and a case can be made for mobilization based on this pedicle rather than the left. In common with others[10,11,13–15] we found no clinical evidence of omental ischaemia from using the left arcade. This method has the advantage of a more direct route to the pelvis, particularly when passed retrocolically, thus increasing the available omental length. Furthermore, separation of the omentum from its attachment to the pancreas and duodenum is not always satisfactory and may result in troublesome bleeding.

We, in common with others[14,16], have had no evidence of early small bowel obstruction, a problem which is often cited as a reason for not placing the omentum in the pelvis. When passed through the transverse mesocolon the omentum lies posteriorly, thus avoiding the risk of creating an axis for small bowel rotation. The omental plug facilitates closure of the pelvic peritoneum and prevents herniation of the gut into the pelvis.

References

1. Fielding LP, Stewart Brown S, Blesowsky L, Kearney G. Anastomotic integrity after operations for large bowel cancer: a multicentre study. *Br Med J* 1980; **281**. 411–14.

2. Smith SRG, Gilmore OJA. Surgical drainage. *Br J Hosp Med* 1985; **33**: 308–11.
3. McLachlin AD, Olsson LS, Pitt DF. Anterior anastomosis of the rectosigmoid colon: an experimental study. *Surgery* 1976; **80**: 306–11
4. Manz CW, La Tendresse C, Sako Y. The detrimental effect of drains on colonic anastomoses. An experimental study. *Dis Colon Rectum* 1970; **13**. 17–45.
5. Crowson WN, Wilson CS An experimental study of the effect of drains on colonic healing. *Am Surg* 1973; **39**. 567–601.
6. Smith SRG, Connolly JC, Crane PW, Gilmore OJA. The effect of surgical drainage materials on colonic anastomotic healing *Br J Surg* 1982; **69**: 153–5.
7. Morrison R. Remarks on some functions of the omentum. *Br Med J* 1906; **1**: 76–9.
8. Kiricuta L. L'utilisation du grand epiploon dans le traitement des fistules post radiotherapeutiques vesico-vaginales, recto-vesico-vaginales et dans les cystoplasties. *J Chir (Paris)* 1965; **89**: 477–84.
9. Turner Warwick RT, Wynne EJC, Handley-Ashken M The use of mental pedicle graft in the repair and construction of the urinary tract. *Br J Surg* 1967; **54**. 849–53.
10. Goldsmith HS Protection of low rectal anastomoses with intact omentum. *Surg Gynecol Obstet* 1977, **144**, 585–6
11 Bunt TJ, Doerhoff CR, Haynes JL. Retrocolic omental pedicle flap for routine plication of abdominal aortic grafts. *Surg Gynecol Obstet* 1984, **158**: 591–2.
12. Dudley HAF, Ratcliffe AG, McGeehan D. Intra-operative irrigation of the colon to permit primary anastomosis. *Br J Surg* 1980; **67**: 80–1.
13. Greenburg BM, Low D, Rosato EF The use of omental pedicled grafts in operations performed upon the colon and rectum. *Surg Gynecol Obstet* 1985; **161**: 487–8.
14. Moreaux J, Horlot A, Barrat F, Mabille J. Obliteration of the pelvic space with pedicled omentum after excision of the rectum for cancer *Am J Surg* 1984, **148**. 641–3.
15 Ruckley CV, Smith AN, Balfour TW. Perineal closure by omental graft. *Surg Gynecol Obstet* 1970; **131** · 300–2
16. Page CP, Charlton PK, Becker DW. Closure of the pelvic and perineal wounds after removal of the rectum and anus. *Dis Colon Rectum* 1980; **23**: 2–9.
17. Zhang Kai, Yang Yihua. Use of pedicled omentum in oesophago-gastric anastomosis: analysis of 100 cases. *Ann R Coll Surg Engl* 1987; **69**: 209–11.
18 Hilsabeck JR. Enterorectal and colorectal anastomosis. Evaluation of techniques including midtransverse or left sided colon tube colostomy and pelvic drainage. *Arch Surg* 1981, **116** · 921–5.
19. Collins CD, Talbot CH. Pelvic drainage after anterior resection of the rectum *Arch Surg* 1969, **99**. 391–3
20. Schwaupp WC. Drainage of low anterior resection. *Am J Surg* 1969; **118**. 627–31
21. Matheson NA, McIntosh CA, Krukowski ZH. Continuing experience with single layer appositional anastomosis in the large bowel. *Br J Surg* 1985, **72** (Suppl.): 104–6.
22. Goldsmith HS, De Los Santos R, Vanamee P, Beattie EJ Experimental protection of vascular prosthesis by omentum *Arch Surg* 1968, **97**: 872–8.
23 Schwab PM, Kelly KA Primary closure of the perineal wound after proctectomy: a new technique. *Mayo Clin Proc* 1974, **49**: 176
24. Elliot MS, Immelman EJ, Stevens PJ D'E Management of the perineal wound with constant irrigation and suction after abdomino-perineal excision of cancer of the rectum *S Afr Med J* 1979; **56**: 796–8
25 Jalan KN, Smith AN, Ruckley CV, Falconer CWA, Small WP, Prescott RJ. Perineal wound healing in ulcerative colitis *Br J Surg* 1969; **56**: 749–53.
26. Broader JH, Masselink BA, Oates GD, Alexander Williams JE. The pelvic space after proctectomy. *Br J Surg* 1974, **61** · 94–7
27. Irvin TT, Goligher JC. A controlled trial of three different methods of perineal wound management following excision of the rectum. *Br J Surg* 1975; **62**: 287–91
28. Gongaware RD, Slanetz CA. Hartmann procedure for carcinoma of the sigmoid and rectum. *Ann Surg* 1973; **178**: 28–30
29. Goligher JC. *Surgery of the Anus Rectum and Colon*, 5th edn. London: Baillière Tindall, 1983
30. ReMine SG. Dozois RR. Harmann's procedure: its use with complicated carcinomas of sigmoid colon and rectum. *Arch Surg* 1981; **116**: 630–3.

Br. J. Surg. 1988, Vol. 75, October,
1016–1018

Pre-operative or postoperative colonic examination for synchronous lesions in colorectal cancer

J. J. T. Tate,
J. Rawlinson*,
G. T. Royle,
F. J. Brunton* and
I. Taylor

University Surgical Unit and
**Department of Radiodiagnosis,*
Southampton General Hospital,
Southampton, UK
Correspondence to:
Mr J. J. T. Tate, University
Surgical Unit, F Level,
Southampton General Hospital,
Tremona Road,
Southampton SO9 4XY, UK

A review of 130 consecutive large bowel examinations at which a cancer of the colon or rectum was diagnosed has been undertaken. Of 50 patients examined by colonoscopy, the whole colon was seen in only 21 (42 per cent) and almost half of these had a tumour in the caecum or ascending colon. In most cases, an incomplete examination was a result of narrowing of the lumen by the tumour preventing passage of the endoscope. Of 80 patients examined by double contrast barium enema, the entire length of the colon was visualized in 83 per cent but the quality of the examination was sufficient to confidently exclude synchronous neoplastic lesions in only 51 per cent. The incidence of synchronous cancer in this series was within the expected range, although two such cancers were not detected until laparotomy, but the incidence of synchronous adenomas was two-thirds of the expected number in colonoscopy patients and one-third in those examined by barium enema. It is concluded that, in patients with known colorectal cancer, pre-operative investigation is unreliable for the detection of all synchronous neoplasia and that patients should have postoperative colonoscopy.

Keywords: Multiple colonic neoplasia, colonoscopy, barium enema

There is a significant risk of synchronous neoplasia in patients being treated for colorectal cancer. Recent reports suggest that the risk is from 4·5 to 9 per cent for a synchronous cancer[1,2] and from 27 to 29 per cent for a synchronous adenoma[3,4]. Often synchronous cancers do not adversely affect the prognosis if they are recognized and treated promptly[5] but, if ignored, present later as a so-called 'early metachronous' growth which may be at a more advanced stage. The significance of synchronous adenomas is not fully understood but their presence is associated with an increased risk of metachronous colorectal cancer[6]. Those in the general population with an adenomatous polyp may have a six-fold increased risk of developing colorectal cancer subsequently[7]. It has been suggested that patients with a primary colorectal cancer require complete eradication of synchronous adenomas to establish a clean colon. Double contrast barium enema (DCBE) is the commonest investigation used to examine the large bowel in the UK but it has failed to demonstrate synchronous tumours in some reported instances[2,5] and, even in expert hands, does miss some small adenomas. Colonoscopy is more accurate for the detection of adenomas <1 cm in size but the importance of such small tumours is uncertain as they may take several years to become overt cancers[8]. It is clear that pre-operative diagnosis of synchronous lesions is preferable as the choice of operative procedure may be affected; however, it is not clear how often a satisfactory examination is possible pre-operatively. A study has been undertaken to determine the quality of pre-operative examination of the large bowel in patients with colorectal cancer.

Patients and methods

A review was carried out of 130 consecutive examinations (80 DCBE and 50 colonoscopy) at which a diagnosis of colorectal cancer had been made and a complete examination of the colon had been attempted. Patients presenting with clinical evidence of intestinal obstruction or those in whom the cancer was confined to a polyp and suitable for endoscopic treatment were not included in the study. The extent of the examination, quality of view obtained and presence of synchronous disease was recorded. The quality of DCBE was determined from the radiologist's report at the time of the examination and was classified into three grades (*Table 1*). The quality of colonoscopy was determined by the endoscopist and similarly graded. In addition, the presence of other benign disease which might affect the ability to recognize synchronous neoplasia (e.g. severe diverticular disease) was noted. The bowel preparation was the same for both procedures and consisted of Picolax® (Ferring AB, Sweden), 1 sachet, and X-prep® (Napp Laboratories, UK), 75 ml, taken together 24 h before the examination and Picolax, 1 sachet, on the morning of the examination.

To assess the results, patients were divided into those with proximal and distal cancers (*Figure 1*). Patients with a proximal cancer would normally be treated by a right hemicolectomy and thus examination of the short segment of bowel proximal to the tumour was not absolutely necessary as it would not affect the management of the patient. For those with a distal cancer, the detection of synchronous neoplasia in the proximal bowel was required as this would not be removed as part of a standard surgical resection. An examination was defined as 'satisfactory' for the purposes of this study if views were obtained which were good enough to confidently exclude neoplasia of the large bowel that would remain after a standard surgical resection of the main cancer.

Results

The site of the cancer in all patients is shown in *Figure 1*; the 80 patients who had DCBE were aged 31–90 (median 70) years, and the 50 who had colonoscopy were aged 28–88 (median 69) years. There was a greater proportion of cancers of the caecum among patients having barium enema but the proportions at other sites were similar.

In the DCBE group there were 30 patients who had a proximal carcinoma; all patients had complete examination of the large bowel but in 5 patients views of the colon distal to the tumour were of poor quality and 3 patients, in whom the technical quality of the films was good, had severe diverticular disease which made identification of synchronous neoplasms difficult in the affected region. Of the 50 patients with a distal tumour, 36 had a complete examination but the quality was

Table 1 *Quality of examination in patients with proximal and distal tumours*

	n	Examination incomplete	Complete but poor views	Complete and good views	'Satisfactory' examination (%)
Proximal tumour					
DCBE	30	0	5	25*	22 (73)
Colonoscopy	11	2	0	9	11 (100)
Distal tumour					
DCBE	50	14	13	23*	19 (38)
Colonoscopy	39	27	0	12	12 (31)

* Seven patients with severe diverticulosis are included in these two groups; DCBE, double contrast barium enema

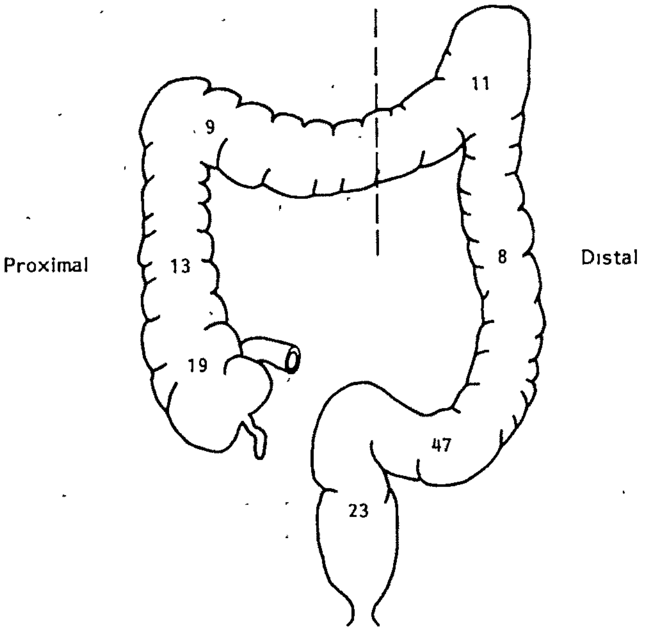


Figure 1 *Distribution of cancer in 130 patients*

Table 2 *Overall results of examination*

Examination	Result	%
DCBE	Complete	83
	Satisfactory	51
Colonoscopy	Complete	42
	Satisfactory	46

DCBE, double contrast barium enema

Table 3 *Grade of doctor performing examination*

	DCBE			Colonoscopy		
	C	SR	R	C	SR	R
Proximal cancer	15	9	6	5	3	3
Distal cancer	21	9	20	16	9	14
Total	36	18	26	21	12	17

DCBE, double contrast barium enema; C, consultants; SR, senior registrar; R, registrar

Table 4 *Pathological classification of cancers*

	DCBE			Colonoscopy		
	A	B	C	A	B	C
Proximal cancers	2	15	13	1	4	6
Distal cancers	7	28	15	5	21	13
Total	9	43	28	6	25	19

DCBE, double contrast barium enema; A, B and C refer to Dukes' classification

poor in 13 of these. In addition, 4 patients with a complete examination of satisfactory quality had severe diverticulosis. Therefore, in all patients having DCBE, synchronous neoplasia could not be excluded in 39 (49 per cent) of 80 patients although complete examination was achieved in 66 (83 per cent) (*Tables 1* and *2*).

Of the 50 patients diagnosed at colonoscopy, 11 had a proximal cancer and in 2 the endoscope was not passed to the caecum but, for the reason given above, effectively all had a satisfactory examination. Among those patients with a distal tumour, 23 could not have complete examination of the colon because the tumour narrowed the lumen sufficiently to prevent passage of the colonoscope. In a further 4 patients, the tumour was passable but a complete examination was not achieved for technical reasons. Therefore, although the quality of view was good in all patients, synchronous lesions could not be excluded in 27 patients (54 per cent) because of incomplete endoscopy (*Tables 1* and *2*).

For all patients, the seniority of the doctor performing DCBE or colonoscopy was similar (*Table 3*) as was the pathological stage of the main cancer, determined by Dukes' classification (*Table 4*). The grade of doctor performing the examination did not appear to have any effect on the result except that in all of the cases diagnosed by colonoscopy in which the tumour was passable but examination was incomplete for technical reasons the endoscopist was a trainee. A cicatrizing cancer that either obstructed the flow of barium (10 patients) or prevented passage of the colonoscope (25 patients) was Dukes' A in 2 patients, B in 19 patients and C in 14 patients which is not greatly different from the overall distribution of Dukes' classification.

The incidence of synchronous cancer was 6 per cent overall. A second cancer was detected in four patients at DCBE and one was missed and discovered at laparotomy (a patient with a proximal rectal cancer who had a complete, satisfactory DCBE showing marked diverticular disease had a synchronous cancer of the proximal sigmoid colon). A second cancer was detected in two patients at colonoscopy and a further one was discovered during laparotomy in a patient who had had incomplete colonoscopy (a patient with a carcinoma of the splenic flexure who had incomplete colonoscopy for technical reasons had a synchronous cancer in the caecum). Synchronous adenomatous polyps were noted in six patients (8 per cent) having DCBE and eight patients (16 per cent) having colonoscopy. The overall incidence of synchronous polyps is not known.

Discussion

In this study both pre-operative DCBE and colonoscopy have been found less than satisfactory for the detection of synchronous neoplasia. Examination of the whole colon and confident diagnosis or exclusion of all synchronous lesions have not been achieved in 49 and 54 per cent respectively. DCBE has allowed a complete examination in most cases but the quality of the examination has been the chief reason for an unsatisfactory result because a small amount of retained faeces can prevent exclusion of synchronous polyps. Although the assessment of quality could have been improved by blind assessment by a single radiologist, the proportion of satisfactory examinations is similar to such a review performed recently in Southampton (J.R., unpublished data) and higher than that achieved at routine DCBE in a recent report from another centre[9]; thus the quality has, if anything, been over-estimated. Effective bowel preparation is of paramount importance for accurate DCBE but the presence of a carcinoma anywhere in the large bowel may, in our opinion, inhibit the effect of preparation; we have observed that marked proximal faecal loading on a plain abdominal film in a patient prepared for DCBE is a sign suggestive of distal stricture. The ability of severe diverticular disease to mask a neoplasm arising in the affected bowel segment is a well-recognized problem of all large bowel contrast radiology[10] and was the reason one synchronous cancer was missed in our study despite good bowel preparation.

With endoscopy the quality of view obtained was satisfactory in all cases in this series because where there was faecal residue present it could be removed or identified as such. However, cicatrizing cancers frequently narrowed the lumen preventing passage of the endoscope. This will not affect the management of the patient with a proximal cancer as adenomas in the distal bowel can still be detected and treated, but the majority of colorectal cancers occur distally and this restricts the number of patients in whom bowel distant to the primary lesion can be examined. In addition, there will be a few patients in whom endoscopy is incomplete because it is technically difficult; a survey of 674 endoscopists in the USA showed the caecum was reached in 75 per cent of diagnostic colonoscopies on average[11].

It is obviously preferable to know in advance if synchronous neoplasms are present; the operative procedure has been altered in 43–88 per cent of patients in whom a synchronous cancer has been discovered in earlier reports[3,12]. Pre-operative DCBE may be better than colonoscopy for detecting a synchronous, proximal cancer because the whole colon is seen in a greater proportion of cases but it cannot be completely relied upon to do so and careful palpation of the whole colon at laparotomy remains essential We are not aware that any cancers were missed among the patients studied but in a large series reported from a specialist centre[13] 33 per cent of synchronous cancers were only discovered when the operative specimen was opened; several patients presented within 3 years of surgery with a metachronous cancer. Our results suggest that DCBE is still less sensitive for the detection of synchronous adenomas and even small ones ($\leqslant 10$ mm) may be of importance[14]. The proportion of patients with a synchronous adenoma who had endoscopic examination was twice that of DCBE, although half the colonoscopies were incomplete, but this difference does not reach statistical significance. However, the incidence of adenomas was lower than that expected, even in the colonoscopy patients, and thus some polyps have probably been missed in both groups.

Intra-operative endoscopy is an alternative method of investigation and should allow both a complete examination and good views in all cases. However, it is time-consuming, adding about 20 min to the operation, technically more difficult than might be expected and adds the risk of further complications to those of the operation; for example distention of the bowel with air during endoscopy can make closure of the abdomen difficult[15]. We feel that intra-operative endoscopy is disruptive, and not entirely reliable; it would be unacceptable to many surgeons, although good results have been described in a small number of cases[16].

It seems unsatisfactory to embark upon long-term follow-up of patients treated for colorectal cancer if the patient has not had thorough investigation for synchronous lesions at the time of primary treatment. Our study shows that, in many patients, pre-operative colonoscopy may be impossible; we do not feel that the group of cancers studied is atypical. Acute presentation of colorectal cancer with established large bowel obstruction is still common and the 'apple-core' appearance of many cancers on radiology demonstrates how narrow the lumen can become in those without symptoms and signs of obstruction. However, it is probably not necessary to modify the operative procedure in every patient with synchronous adenomas as these can be treated endoscopically at a later date. It has been suggested that such patients should have total colectomy and ileocolic anastomosis[17], but we agree with others who favour such radical treatment only in younger patients with multiple adenomas[2].

We conclude that, in a patient known to have colorectal cancer, pre-operative investigation to exclude synchronous neoplastic lesions may be of little value. We suggest that all patients, especially those who have not had previous endoscopic examination of the whole remaining large bowel, should have postoperative colonoscopy.

References

1 Abrahams JS, Reines HD. Increasing incidence of right-sided lesions in colorectal cancer *Am J Surg* 1979, **137**: 522–6.

2. Cunliffe WJ, Hasleton PS, Tweedle DF, Schofield PF. Incidence of synchronous and metachronous colorectal cancer. *Br J Surg* 1984; **71**: 941–3

3. Askew A, Ward M, Cowen A. The influence of colonoscopy on the operative management of colorectal cancer. *Med J Aust* 1986; **145**. 254–5.

4. Isler JT, Brown PC, Lewis FG, Billingham RP. The role of preoperative colonoscopy in colorectal cancer *Dis Colon Rectum* 1987, **30**: 435–9.

5 Heald RJ, Bussey HJR Clinical experiences at St. Mark's Hospital with multiple synchronous cancers of the colon and rectum. *Dis Colon Rectum* 1975; **18**: 6–10.

6. Muto T, Bussey HJ, Morson BC The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**: 2251–70.

7 Kune GA, Kune S, Watson LF History of colorectal polypectomy and risk of subsequent colorectal cancer. *Br J Surg* 1987; **74**: 1604–5.

8. Hoff G. Colorectal polyps. *Scand J Gastroenterol* 1987; **22**. 769–75.

9 Lindsay DG, Freeman JG, Cobdn I, Record CO Should colonoscopy be the first investigation for colonic disease. *Br Med J* 1938, **296**: 167–9.

10. Boulos PB, Karamanolis DG, Salmon PR, Clark CG Is colonoscopy necessary in diverticular disease? *Lancet* 1984; i: 95–6

11. Gilbert DA, Shaneyfelt SL, Silverstein FE *et al*. The national ASGE colonoscopy survey. *Gastrointest Endoscopy* 1984, **30**. 143.

12. Langevin JM, Nivatvongs S. The true incidence of synchronous cancer of the large bowel: a prospective study. *Am J Surg* 1984; **147**: 330–3.

13. Finan PJ, Ritchie JK, Hawley PR. Synchronous and 'early' metachronous carcinoma of the colon and rectum. *Br J Surg* 1987; **74**. 945–7.

14. Church JM, Fazio VW, Jones IT. Small colorectal polyps are they worth treating *Dis Colon Rectum* 1988; **31**: 50–3

15. Colin-Jones DG. Investigating gastrointestinal bleeding of uncertain origin. *GI Futures and Clinical Practice* 1988; **3**: 10–12.

16 Kaibara N, Kimura O, Nishidoi H, Miyano Y, Koga S Intraoperative colonoscopy for the diagnosis of multiple cancers of the large intestine *Jpn J Surg* 1982, **12**. 117–21.

17. Wright HK, Thomas WH, Cleveland JC. The low recurrence rate of colonic carcinoma in ileo-colic anastomosis *Surg Gynecol Obstet* 1969; **129**: 960–2.

Br. J. Surg. 1988, Vol. 75, October,
1019–1022

Endoluminal ultrasound and computed tomography in the staging of rectal cancer

P. J. Holdsworth,
D. Johnston,
A. G. Chalmers*,
P. Chennells*,
M. F. Dixon†,
P. J. Finan,
J. N. Primrose and
P. Quirke†

University Departments of Surgery,
*†Pathology and *Department of*
Radiology, The General Infirmary,
Great George Street, Leeds
LS1 3EX, UK
Correspondence to:
Professor D. Johnston

Pre-operative staging of rectal cancer might define patients with disease confined to the rectal wall without lymph node metastases, in whom local excision might be appropriate, or patients with extrarectal spread, who might benefit from pre-operative radiotherapy. With these objectives, 36 consecutive patients with rectal cancer were studied by endoluminal ultrasound: 17 of them also underwent computed tomography (CT) of the pelvis. The results were correlated with the findings at operation and subsequent pathological examination. Endoluminal ultrasound correctly predicted invasion of the tumour through the rectal wall in 86 per cent of patients, with a sensitivity of 96 per cent and specificity of 50 per cent, but correctly identified lymph node metastases in only 61 per cent of patients (sensitivity 57 per cent; specificity 64 per cent). CT correctly predicted invasion through the rectal wall in 94 per cent of cases, with a sensitivity of 100 per cent and specificity of 67 per cent and correctly identified lymph node metastases in 70 per cent of patients (sensitivity 25 per cent; specificity 85 per cent). These findings indicate that both endoluminal ultrasound and CT may be helpful in selecting patients for pre-operative radiotherapy. Neither technique, however, can reliably identify lymph node metastases and therefore cannot be used to select patients who would be suitable for local excision.

Keywords: Rectal cancer, computed tomography, endoluminal ultrasound, pre-operative staging

The extent of surgical resection of the rectum for rectal cancer is limited by the pelvic side walls and by adjacent pelvic viscera. These anatomical limitations help to explain the incidence of local recurrence, which ranges from 2 per cent to 43 per cent[1]. Adjuvant therapy might improve these figures, particularly in the case of locally advanced tumours for which surgical excision with a wide margin is not feasible. Pre-operative, low dose radiotherapy appears to offer little benefit in terms of local recurrence, but recent reports of the use of higher dose regimens suggest that the incidence of local recurrence may indeed be reduced[2–4].

At the other end of the disease spectrum is a group of patients who have rectal cancers that are confined to the rectal wall. They are potentially curable by means of local therapy by peranal techniques, providing that pre-operative staging is sufficiently accurate[5]. However, selection of suitable patients for local excision is rendered difficult at present by reports that some patients with disease that is apparently confined to the rectal wall have lymph node metastases[6].

Thus, accurate pre-operative staging of malignant disease is essential for the formulation of appropriate strategies for the management of individual patients. Staging techniques must be able to define accurately the extent of local disease and detect the presence of metastases. In the case of rectal cancer, this implies that the technique must be capable of distinguishing between disease confined to the rectal wall and disease extending into perirectal tissues. It must also be able to detect lymph node metastases, both in the perirectal tissues and on the side walls of the pelvis.

The aim of this study was to assess the ability of endoluminal ultrasound and computed tomography (CT) to fulfil these staging requirements in patients with rectal cancer.

Patients and methods

Thirty-six consecutive patients with primary rectal cancer were studied. Each patient underwent pre-operative endoluminal ultrasound examination and 17 of them also had a CT scan performed. Details of the patients are given in *Table 1*. All patients had histologically proven rectal cancer which was subsequently treated surgically by standard radical techniques, either abdominoperineal excision (38 per cent) or sphincter-saving excision (62 per cent).

The distribution of the primary tumours in the rectum is shown in *Table 2*.

Endoluminal ultrasound

Endoluminal ultrasound was carried out by one radiologist (P.C.) by means of a 5·5 MHz radial scanner (Bruel and Kjaer, Denmark). Each scan was carried out with the patient in the left lateral position after rectal washout if necessary. The ultrasound probe was inserted per rectum to the site of the tumour. A latex balloon surrounding the transducer was then inflated with 40–60 ml of degassed water. The transducer rotated at 2–6 cycles per second. Views of the tumour were obtained in all cases, although when the rectal lumen was narrowed

Table 1 *Details of patients*

	Patients
Number	36
Age (years)*	70 (48–88)
Male:female	21:15
Sphincter-saving resection (%)	62
Abdominoperineal excision (%)	38

* Median (range)

Table 2 *Site of primary tumour*

	Endoluminal ultrasound	Computed tomography
Upper third	7	4
Middle third	13	5
Lower third	16	8

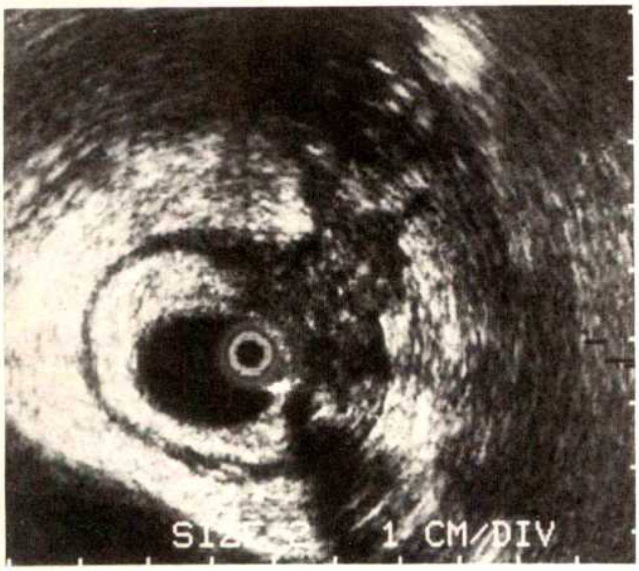


Figure 1 *Endoluminal ultrasound scan showing an extensive rectal tumour invading through the rectal wall into the perirectal fat*

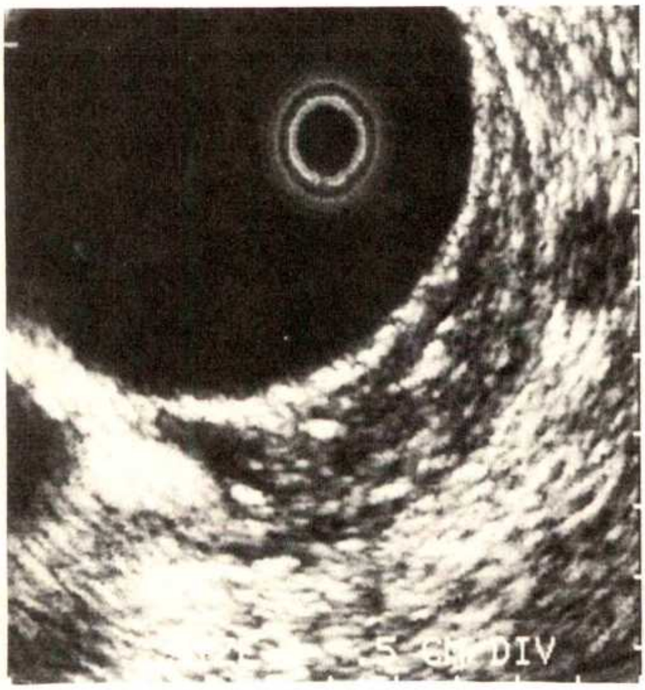


Figure 2 *Endoluminal ultrasound scan showing a rectal tumour confined to the rectal wall with an adjacent lymph node which on pathological examination was not involved with tumour*

the full extent of the tumour could not always be visualized and only the inferior aspect could be assessed. Representative views of the tumour were stored on photographic plates.

CT

CT was performed by one radiologist (A.G.C.) using a third generation scanner (International General Electric 9800). Each patient was prepared for the scan by oral administration of 1 litre of a 3 per cent solution of sodium diatrizoate and meglumine diatrizoate (Gastrografin, Schering Health Care, Sussex, UK) 1 h before the examination, after conventional bowel preparation. The rectum was outlined with either 400 ml of 1 per cent sodium diatrizoate solution (Hypaque, Sterling Research Labs, Surrey, UK) or by air insufflation. With the patient prone on the examination table, targeted contiguous 5 mm slices, or 5 mm slices at 10 mm intervals, were obtained from the symphysis pubis to the mid-sacroiliac joints or beyond the upper limit of the tumour.

Staging definitions

Endoluminal ultrasound. The depth of invasion of the primary tumour was assessed and the patients divided into two groups depending on penetration of the tumour outside the rectal wall (*Figures 1* and *2*).

Tumour staging using the TNM classification was not used because CT was unable to define clearly the individual layers of the rectal wall. Lymph node status was assessed using the fact that nodes had been demonstrated as presumptive evidence that they were involved with tumour, since it was impossible to predict which of any visible lymph nodes harboured metastases.

CT. The primary tumour was assessed by defining patients in whom the tumour was considered to have invaded through the rectal wall (*Figure 3*) and patients in whom the tumour was confined to the wall (*Figure 4*). Lymph node status was determined using standard CT criteria and lymph nodes were said to contain metastases if they measured more than 1·5 cm in the transverse axis[7].

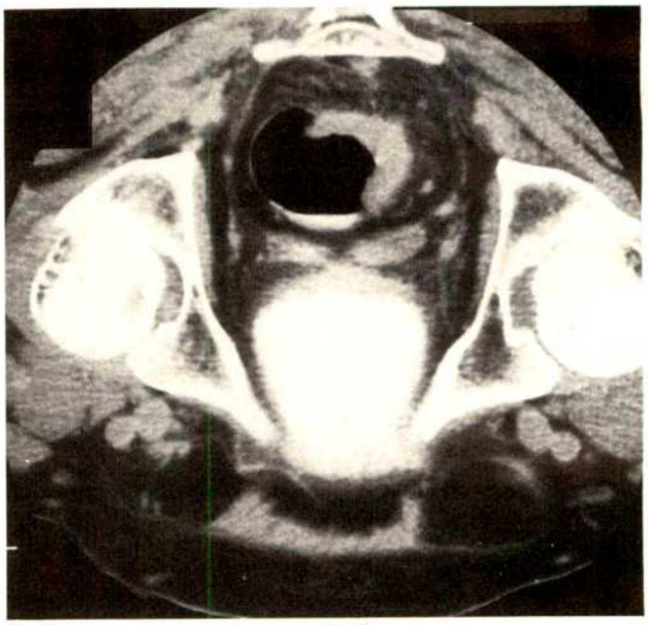


Figure 3 *Computed tomography scan showing a rectal tumour infiltrating the perirectal fat*

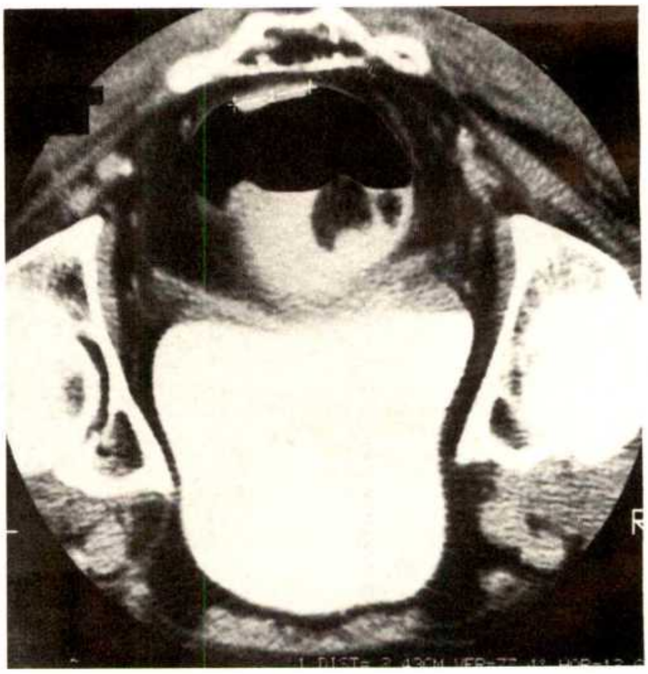


Figure 4 *Computed tomography scan showing a rectal tumour* (*marked*) *confined to the rectal wall*

The results of these staging procedures were correlated with the histopathological stage of the resected specimen in order to define their accuracy.

Results

Primary tumour

Endoluminal ultrasound correctly identified 27 tumours that had invaded through the rectal wall and understaged 1 patient, giving a sensitivity of 96 per cent. Eight patients had tumours that were confined to the rectal wall: endoluminal ultrasound correctly identified only four of them, thereby overstaging the other four, giving a specificity of 50 per cent (*Table 3*).

Of the 17 patients who underwent CT scanning, 14 had tumours extending through the rectal wall and all 14 were correctly identified (sensitivity 100 per cent). Of the remaining 3 patients, 2 were diagnosed correctly as having tumours confined to the rectal wall and there was 1 false positive (*Table 3*).

Lymph node status

Using the above criteria, endoluminal ultrasound correctly predicted that lymph nodes were involved with tumour in 8 of 14 patients (sensitivity 57 per cent), and correctly diagnosed the absence of metastases in lymph nodes in 14 of 22 patients, giving a specificity of 64 per cent (*Table 4*).

Table 3 *Assessment of tumour invasion through the rectal wall*

	Endoluminal ultrasound	Computed tomography
Predicted: Invasion through wall Pathology: Invasion through wall	27	14
Predicted: Invasion through wall Pathology: Confined to the wall	4	1
Predicted: Confined to the wall Pathology: Invasion through wall	1	0
Predicted: Confined to the wall Pathology: Confined to the wall	4	2

Table 4 *Assessment of lymph node status*

	Endoluminal ultrasound	Computed tomography
Predicted: Lymph node +ve Pathology: Lymph node +ve	8	1
Predicted: Lymph node +ve Pathology: Lymph node −ve	8	2
Predicted: Lymph node −ve Pathology: Lymph node +ve	6	3
Predicted: Lymph node −ve Pathology: Lymph node −ve	14	11

CT proved no better than endoluminal ultrasound at defining disease in lymph nodes, being able to pick out only one of four patients who had nodal metastases. However, CT overstaged only 2 of 13 patients who did not have metastases in lymph nodes, giving a specificity of 85 per cent (*Table 4*).

The overall results of these two staging techniques are shown in *Table 5*.

Discussion

There have been several encouraging reports recently describing the high degree of accuracy of endoluminal ultrasound for pre-operative tumour staging of rectal cancer[8–10]. The role of CT in staging rectal cancer has also been assessed either alone or in combination with endoluminal ultrasound. In general, the tumour staging accuracy of the two techniques is similar, although there remains some dispute as to the ability of CT to stage tumours using the TNM system[7,9–13]. However, the influence of such detailed tumour staging on the treatment of patients with rectal cancer remains in question[14].

Two factors that may influence clinical decision making are the presence or absence of tumour invasion beyond the rectal wall and the presence or absence of lymph node metastases. Extensive local invasion can usually be detected by the experienced examiner's finger, although tumour fixity can on occasion misrepresent the extent of the disease if the tumour has provoked an intense inflammatory reaction[11,15]. Both endoluminal ultrasound and CT were found to define local invasion with a high degree of accuracy in this study and could therefore be used to select patients who would be suitable for adjuvant radiotherapy.

Tumours that are confined to the rectal wall present a different problem in management. Although most of the patients with this type of tumour are cured by radical surgery, such as abdominoperineal excision or low anterior resection, there is a subgroup of patients in whom such major and radical surgery is unnecessary to obtain a cure. The potential benefits to patients who could be cured by local excision are obvious. In keeping with other reports, our results have shown that both endoluminal ultrasound and CT are able to detect tumours that remain confined to the rectal wall, although CT in this study proved unable to define precisely the exact depth of invasion: however, this may be of little relevance to patient management. A more major problem, which makes selection of patients for local excision very difficult and indeed dangerous, is the knowledge that up to 14 per cent of patients with a primary tumour that appears to be confined to the rectal wall will have lymph node metastases[6]. It is vital, therefore, that staging techniques should be able to define lymph nodes that are involved with tumour. We found that lymph nodes were frequently visible on endoluminal ultrasound, but that this finding was a poor predictor of whether the nodes demonstrated actually contained tumour metastases (*Figure 2*). The use of more refined criteria might improve the ability of endoluminal ultrasound to define the status of lymph nodes more accurately. CT also proved incapable of detecting lymph node metastases with sufficient accuracy to permit a confident choice of local

Table 5 *Overall results*

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Invasion through the rectal wall					
Endoluminal ultrasound	96	50	87	80	86
Computed tomography	100	67	93	100	94
Lymph node metastases					
Endoluminal ultrasound	57	64	50	70	61
Computed tomography	25	85	33	78	70

ablative therapy to be made, although most of the nodes less than 1·5 cm diameter were not involved with tumour. Pelvic lymph nodes can occasionally be mistaken for blood vessels and an intravenous bolus of contrast can be used to make the distinction.

In summary, the use both of endoluminal ultrasound and of CT gives a more accurate picture of the local extent of a rectal cancer than does clinical examination alone. Nevertheless, the margin of error that we found with these techniques, particularly for identifying lymph node metastases, is such that at present their influence on the management of individual patients remains, at best, marginal.

References

1. Goligher JC. Neoplasms: surgical treatment. *Current Opinion in Gastroenterology* 1985; **1**: 41–50.
2. Stockholm Rectal Cancer Study Group. Short term pre-op radiotherapy for adenocarcinoma of the rectum. *Am J Clin Oncol* 1987; **80**: 369–75.
3. Lise M, Gerard A, Nitti D *et al.* Adjuvant therapy for colorectal cancer. The EORTIC experience and a review of the literature. *Dis Colon Rectum* 1987; **30**: 847–54.
4. Duncan W. Pre-operative radiotherapy in rectal cancer. *World J Surg* 1987; **11**: 439–45.
5. Mann CV. Techniques of local surgical excision for rectal cancer. *Br J Surg* 1985; **72**, Suppl: S57–8.
6. Dukes CE, Bussey HJR. The spread of rectal cancer and its effect on prognosis. *Br J Cancer* 1958; **12**: 309–20.
7. Williams MP, Husband JE. CT scanning in carcinoma of the rectum: a review. *J R Soc Med* 1987; **80**: 701–3.
8. Beynon J, Foy DMA, Roe AM, Temple LN, Mortensen NJMcC. Endoluminal ultrasound in the assessment of local invasion in rectal cancer. *Br J Surg* 1986; **73**: 474–7.
9. Kramann B, Hildebrandt U. Computed tomography *versus* endosonography in the staging of rectal carcinoma: a comparative study. *Int J Colorect Dis* 1986; **1**: 216–18.
10. Romano G, de Rosa P, Vallone G, Rotondo A, Grassi R, Santangelo ML. Intrarectal ultrasound and computed tomography in the pre- and postoperative assessment of patients with rectal cancer. *Br J Surg* 1985; **72**, Suppl: S117–19.
11. Williams NS, Durdey P, Quirke P *et al.* Pre-operative staging of rectal neoplasm and its impact on clinical management. *Br J Surg* 1985; **72**: 868–74.
12. Rifkin MD, Wechsler RJ. A comparison of computed tomography and endorectal ultrasound in staging rectal cancer. *Int J Colorect Dis* 1986; **1**: 219–23.
13. Dixon AK, Kelsey Fry I, Morson BC, Nicholls RJ, York Mason A. Pre-operative computed tomography of carcinoma of the rectum. *Br J Radiol* 1981; **54**: 655–9.
14. Hawley PR. Commentary: does rectal endosonography influence rectal cancer treatment? *Int J Colorect Dis* 1986; **1**: 224–6.
15. Nicholls RJ, York Mason A, Morson BC, Dixon AK, Kelsey Fry I. The clinical staging of rectal cancer. *Br J Surg* 1982; **69**: 404–9.

Fine Needle Aspiration of the Breast

Yolanda C Oertel MD
Professor of Pathology, The George Washington University, School of Medicine, Washington DC, USA.

- ★ **Clearly and concisely written with extensive illustrations including many in colour**
- ★ **Cover all the aspects of the technique from performance to evaluation**
- ★ **Essential reading for surgical pathologists involved in performing aspirations**

Fine needle aspiration is a valuable diagnostic tool that is gaining increased acceptance in the United States. It helps clinicians and surgeons arrive at a more accurate diagnosis in a timely and economical fashion and enhances their ability to manage patients more effectively. This monograph is the product of nine years' experience in which about 10,000 aspirates were interpreted or performed. It covers all aspects of the technique, from performance of the aspiration and processing the specimen, to the evaluation of the information obtained from the procedure. As this experience has shown that results are superior when the aspiration is performed by the pathologist, the emphasis throughout is on the technical aspects of the procedure. The text is extremely well illustrated to facilitate evaluation and differentiation of findings. The result is a clearly written, practical guide to fine needle aspiration of the breast.

Contents

Introduction • Advantages and disadvantages of needle aspiration • Questions asked more frequently • Fine needle aspiration technique • How to succeed at fine needle aspiration • Usual findings in the aspirates • Occasional findings in the aspirates • Benign lesions • Atypical ductal hyperplasia • General diagnostic criteria of malignancy • Adenocarcinomas • Malignant nonepithelial neoplasms • Metastic tumors in the breast • Thoracic wall recurrences and axillary masses • Pitfalls • Fine needle aspiration of nonpalpable breast lesions • Additional diagnostic information • Statistical summary • References • Index

1987 232 pages 260 × 180mm Hardcover Illustrated 0 409 95192 7 £60.00 Butterworths USA

Order this title from your usual bookseller or in case of difficulty complete the coupon below.

Order Form

To: Butterworth & Co (Publishers) Ltd, Borough Green, Sevenoaks, Kent TN15 8PH, UK. Telephone: (0732) 884567 Telex: 95678

24 Hour Order Line: (0732) 882566 – This line gives immediate access at any hour. Orders can be placed over the telephone by using your Butterworths account number or by charging to your credit account.

Cash or credit card details with order are essential except for account customers. Overseas orders not accompanied by a remittance will be charged postage and packing.

Please send me .... copy(ies) of: **Fine Needle Aspiration of the Breast** 0 409 95192 7 £60.00

Please select preferred method of payment:
☐ I enclose remittance for £ ....
☐ Please debit my credit card as follows
☐ Access/Mastercard ☐ Barclaycard and other Visa cards
☐ American Express

Card Number
Expiry Date ________ Signature ________
☐ Please include me on your mailing list.

Name ________
Position ________
Address ________
____
____
________ Postcode ________

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. In the UK please allow 21 days for delivery.

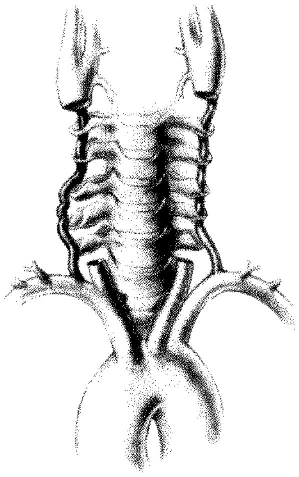
Registered office: 88 Kingsway, London, WC2B 6AB.
Registered in England No 125354

Butterworths
meeting professional needs
BOROUGH GREEN SEVENOAKS KENT TN15 8PH UK

NEW FROM BUTTERWORTHS . . .

Atlas of Duplex Ultrasonography

Sergio X Salles-Cunha PhD **George Andros** MD



★ **the definitive reference for vascular surgeons, medical physicists and radiologists**

★ **high quality duplex scans correlated with explanatory diagrams, arteriograms and surgical specimens**

★ **offers practical guidance for optimum results**

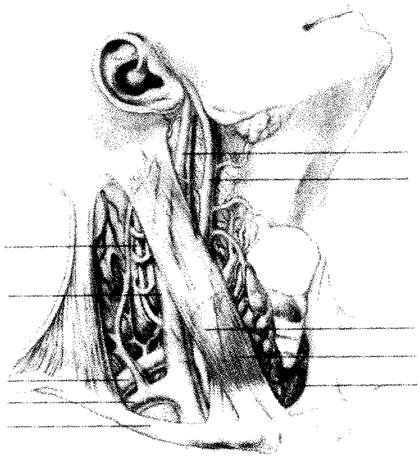
★ **combines the experience and expertise of leading clinical and research laboratories**

Concise Contents:

Arterial Studies · Extracranial Cerebrovasculature in the Neck · Lower extremities · Abdomen · Upper extremities · **Venous Scanning** · Lower extremities · Upper extremities · **Special Studies** · Appendix 1 · Appendix 2

May 1988 192 pp 203 x 235 mm
Hardcover Illustrated 0 941022 08 0
£60.00
A Butterworths/Appleton Davies publication

Please order this title from your usual bookseller or in case of difficulty use the coupon below.



Butterworths

ORDER FORM

To: Felicity Davie, Butterworth Scientific Ltd, PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK
Cash or credit card details with order are essential except for account customers. Overseas orders not accompanied by a remittance will be charged postage and packing.

Please send me ________ copy(s) of **Atlas of Duplex Ultrasonography** 0 941022 08 0 £60.00

Please select preferred method of payment:

☐ I enclose remittance for £ ________

☐ Please debit my credit card as follows

☐ Access ☐ Barclaycard and other Visa cards ☐ American Express

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry Date ________ Signature ________

☐ Please include me on your mailing list

Name ________

Position ________

Address ________

____

________ Postcode ________

All prices are subject to change without notice and orders are subject to acceptance by Butterworths Head Office. In the UK please allow 21 days for delivery.
Registered office: 88 Kingsway, London WC2B 6AB Registered in England No 125354

Butterworths
meeting professional needs

Br. J. Surg. 1988, Vol. 75, October, 1023–1033

Preventing wound infection after appendicectomy: a review

Z. H. Krukowski,
S. T. Irwin,
S. Denholm and
N. A. Matheson

Department of Surgery,
University of Aberdeen,
Aberdeen, UK
Correspondence to:
Mr Z. H. Krukowski, Department of Surgery, Medical School, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZD, UK

An exponential increase in the number of published prospective studies reflects both a continuing interest in, and a lack of consensus on, the optimal prophylaxis of wound sepsis after appendicectomy. Review of the literature over the last 25 years leads us to emphasize both the importance of adequate study size and of stratification of the severity of the sepsis found at operation. For critical comparison of prophylactic regimens the high percentage of wound infections disclosed after discharge from hospital must be taken into account. Antibiotics reduce the frequency of wound sepsis and although low wound sepsis rates have been reported with systemic antibiotics active against only anaerobes, the cumulative evidence favours a spectrum of antibacterial activity against both aerobic and anaerobic organisms. Topical antiseptics have no significant effect but topical antibiotics are beneficial. Wide variations in outcome for similar antibiotic regimens reflect the importance of technical factors in determining the frequency of wound sepsis.

Keywords: Postoperative wound infection, appendicectomy

A wide range of developing and established peritoneal sepsis is encountered in operations for acute appendicitis. Contamination of the abdominal wound by pathogens derived from the normal appendicular microbial flora is therefore a frequent accompaniment of emergency appendicectomy and wound infection is the commonest source of postoperative morbidity. The frequency of wound infection is a function of the degree of operative contamination[1–6] and various manoeuvres are used either to minimize contamination or to mitigate its consequences. The purpose of this review is critically to analyse relevant published work to identify measures for which there is convincing evidence of benefit.

A literature survey covering the last 25 years was carried out. Papers reporting the results of retrospective or anecdotal experience were in general excluded although some are discussed because of particular interest. The majority of publications reviewed are reports of prospective studies. The increase in the number of publications during the past 25 years reflects the absence of a universally acceptable solution to the problem of wound sepsis after appendicectomy (*Figure 1*).

The scientific ideal of a 'fair' experiment in which only one variable is examined is seldom attainable in a clinical context in which many variables inevitably intrude. The unwelcome influence of such variables can be reduced only by their allocation in equal measure to the compared groups. The need to recruit sufficient patients into comparative studies of surgical procedures[7] and the potential for error in interpreting the outcome of small studies is well known[8]. The numbers in published papers, however, are often small and vary widely (median 147 cases; range 29–864), and the total number was less than 200 in 66 per cent of reports. The problem of the size of a study is compounded by the stratification of patients into differing risk categories and by allocation to a variety of treatment groups, as many as six in some studies[9]. Although there are inevitably differences in the management of patients from different centres, in the absence of any declared deviation from 'conventional' treatment we have grouped together cases treated in a similar fashion. We have also defined the risk of wound infection as low or high according to the criteria in *Table 1*.

Definition of wound infection

Ljungqvist's definition of wound infection[10], the discharge of pus or positive bacteriological culture from a wound discharge, has been widely adopted and was used. A 'stitch' abscess, remote from the incision, or erythema which did not progress

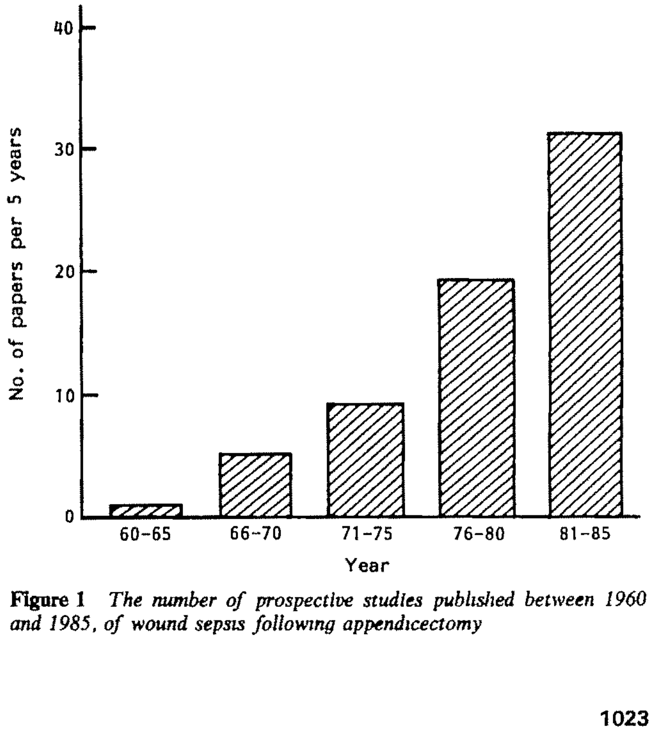


Figure 1 *The number of prospective studies published between 1960 and 1985, of wound sepsis following appendicectomy*

to suppuration were excluded. This definition is simple for wound infections developing in hospital but from 13 to 66 per cent[11–16] of infections present after the patient has been discharged and 'in-hospital' wound infection rates seriously underestimate the true frequency. Although many 'late' wound infections are trivial, adequate follow-up information is necessary for critical analysis of wound infection rates when comparing antibiotic regimens. Antibiotics may delay the presentation of wound sepsis until after the patient has been discharged without altering the overall incidence[17–20], an important point in appendicitis after which postoperative stay is generally short. Ideally, all patients entered in a prospective study of wound sepsis should be reviewed at approximately 4 weeks after the operation to detect evidence of late sepsis. The quality of the follow-up data has, in fact, improved remarkedly during the period of this review.

Operative contamination

The reported overall frequency of wound sepsis in control groups of patients after appendicectomy varies between 5 per cent and 33 per cent (*Table 2*) and the degree of operative contamination of the wound is one of the most important determinants.

A combination of quantitative and qualitative bacteriology of a wound, i.e the concentration[39] and types of organisms present[9,40,41], should give the best correlation with the risk of postoperative wound sepsis, but quantitative bacteriology is laborious and has not been attempted in any clinical studies of wound infection after appendicectomy. Qualitative bacteriology, in contrast, and the relationship between organisms cultured from the operative field and subsequent wound infection, have been routine in most recent studies.

Table 1 *Operative classification of contamination during appendicectomy*

1 Low risk
    Normal
    Inflammation without suppuration
2. High risk
    Gangrenous appendicitis
    Perforated appendicitis
        Abscess formation
        Localized peritonitis
        Diffuse peritonitis

Before 1974 enteric coliform organisms were thought to be the commonest pathogens present in appendicitis[2,23,39], but since then the role of anaerobes has been emphasized. In a study of 322 consecutive patients undergoing emergency appendicectomy[69], organisms were cultured from 47·5 per cent of swabs taken from the appendix fossa. Surprisingly, the frequency of recovery of pathogens was the same when the appendix was normal (45 per cent), fibrotic (41 per cent), acutely inflamed but not perforated (44 per cent) or involved in lymphoid hyperplasia (45 per cent). The percentage of positive cultures increased to 79 per cent in patients with perforated appendicitis. *Bacteroides* species were identified in 78 per cent of all positive cultures (72 per cent in perforated cases) and in 93 per cent of infected wounds.

Subsequent bacteriological studies have not reported comparably high rates of identification of anaerobes in either perforated[6,14,42,43] or non-perforated appendicitis[6,14,33,38]. Lower identification rates may either be an accurate representation of the bacteriology or reflect differences in bacteriological technique[41] but an alternative explanation is that few contemporary studies include control groups not given antibiotic prophylaxis, particularly if a pre-operative diagnosis of perforation has been made. Pre-operative antibiotics have a profound effect on the rate of recovery of viable intraperitoneal bacteria in peritonitis[44] and contemporary reports on the bacteriology of appendicitis should be interpreted in this light. The re-emergence in the 1980s of aerobic pathogens as the most common organisms encountered in the peritoneum and wound[6,14,33,43,45–50] may reflect the widespread use of anti-anaerobic agents. The ability of antibiotics to alter the spectrum of pathogens recovered is of some concern if it leads to the emergence of more virulent organisms[51].

In an individual patient, bacteriology gives the best indication of the risk of wound sepsis but is of little practical value because the results of culture and sensitivity testing are not available for 24–48 h after the operation. The contaminating organisms may be predicted with accuracy but determination of the risk of

Table 2 *Wound sepsis rates in control groups*

		Low risk			High risk			Overall		
First author	Year	(No.)	(WI)	(%)	(No.)	(WI)	(%)	(No.)	(WI)	(%)
Bird[21]	71	66	23	34·8	18	2	11·1	84	25	29·8
Andersen[22]	71	187	16	8·6						
Mackie[23]	73	23	2	8·7	10	7	70·0	33	9	27·3
Gilmore[24]	74	110	10	9·1	41	14	34·1	151	24	15·9
Willis[3]	76	39	9	23·1	7	2	28·6	46	11	23·9
Leigh[4]	76	100	17	17·0				100	17	17·0
Everson[25]	77	85	7	8·2	41	27	65·9	126	34	27·0
Tanphiphat[26]	78	104	3	2·9	20	9	45·0	124	12	9·7
Donovan[27]	79	63	17	27·0	9	7	77·8	72	24	33·3
Morris[13]	80	61	15	24·6	5	5	100·0	66	20	30·3
Pettigrew[28]	81				41	15	36·6			
Lau[29]	81							108	26	24·1
Busittil[30]	81							45	6	13·3
Kortelainen[31]	82	115	8	7·0	39	9	23·1	154	17	11·0
Hutchinson[32]	83							66	11	16·7
Keiser[33]	83	38	3	7·9	2	1	50·0	40	4	10·0
Gledhill[34]	83	40	3	7·5	20	9	45·0	60	12	20·0
Chiam[6]	83							74	20	27·0
Winslow[35]	83	52	5	9·6						
Viitanen[35]	84	125	6	4·8	52	15	28·8	177	21	11·9
Kling[37]	85	39	3	7·7	36	9	25·0	75	12	16·0
El-Sefi[16]	86	93	9	9·7	7	4	57·1	100	13	13·0
Eklund[38]	87	192	4	2·1	65	9	13·8	257	13	5·1
Total		1532	160	10·4	413	144	34·9	1958	331	16·9

WI, wound infection

sepsis depends on clinical stratification according to the degree of inflammation at operation. Most authors acknowledge the greatly increased risk of wound sepsis when the appendix is gangrenous or perforated, and analyse their results accordingly. Patients with severe peritoneal contamination or diffuse peritonitis, however, are often excluded from prospective studies of 'prophylactic' antibiotics because alternative therapeutic regimens have been used. This review considers wound infection rates in both the low- and high-risk categories (*Table 1*) and when information on excluded cases given supplementary antibiotics has been presented it is also discussed.

Delay in diagnosis

If acute appendicitis were to follow a relentless progression from intramural inflammation through luminal obstruction to gangrene, perforation and abscess formation or peritonitis, delay in diagnosis should be a significant factor in the frequency of postoperative sepsis. Only one paper has supported this hypothesis[29] and has shown a 60 per cent increase in wound sepsis when the history of abdominal pain was longer than 48 h. This relationship was not confirmed in two other studies[13,42]. The progression of acute appendicitis is probably variable and may be delayed or halted by host defences, with spontaneous resolution, at any point in its evolution. The safety of 'active observation'[52] in undiagnosed abdominal pain no doubt depends on this variable biological response. The higher rate of wound sepsis associated with an increased frequency of gangrenous and perforated appendicitis at the extremes of age[29,53,54] may reflect delay in presentation or diagnosis or, perhaps, more rapid progression of the disease in the very old or very young.

Influence of operative technique

The dependence of outcome of any operation on operative difficulty, technique and operating skill has been an infrequently stated consideration but there is evidence of reassertion of the importance of the conduct of an operation in relation to postoperative morbidity[55,56]. In so far as appendicectomy has traditionally been the province of the most junior operator in a team it would not be surprising if high complication (wound infection) rates were a consequence[23,24]. We may all readily visualize a difficult emergency appendicectomy performed in the middle of the night with inadequate assistance through an inappropriately sited incision and appreciate the potential role of tissue trauma and operative contamination on the risk of subsequent wound sepsis. Although the assessment of difficulty is subjective, if the operator judges an operation to have been technically difficult, wound infection rates increase[29].

The influence of operative technique on wound sepsis has from time to time been emphasized[1,57–60] and the importance of haemostasis and gentle technique have been stressed[6,57]. Reduction in the degree of bacterial contamination and the avoidance of favourable conditions for bacterial proliferation are probably the most relevant consequences of meticulous technique. If wound contamination can be avoided, wound sepsis is rare[1–3,25]. Conversely, increasing degrees of bacterial contamination of the operative field (demonstrated by bacteriological sampling of the peritoneum and wound) are associated with an eightfold increase in wound sepsis from 7 per cent if bacterial contamination is present in only one site[2,6] to 54 per cent when both sites are contaminated[1,2,28,61].

Most appendicectomies are performed through a variant of the grid-iron incision but this may be inappropriate when diffuse peritonitis is present[62]. It is more difficult to protect the edges of a small grid-iron incision from contamination than a more generous vertical incision which exploits the easier application of wound towels and plastic ring drapes[63], particularly when considerable retraction and manipulation result from an inadequate or poorly sited incision. The problem is compounded in the obese, who may also suffer an excessive frequency of perforated and gangrenous appendicitis[53]. Wound protection by antiseptic-soaked gauze has been recommended and is associated with low wound-infection rates[1,2,57]. The practical problem of retaining them in position during manipulation may require suture to the wound edges[57].

Omission of inversion of the ligated appendix stump does not increase wound sepsis and has the attraction of simplification of the procedure without apparent detriment[64,65]. In contrast, closure of the skin with a continuous subcuticular suture more than doubles the incidence of wound infection compared with an interrupted technique[66].

Drains

The use of drains after appendicectomy is variable and they are usually only thought to be indicated for perforated appendicitis. Drainage of the peritoneal cavity, in contrast to a localized abscess cavity, is not only ineffective[67] but positively detrimental in terms of delayed recovery[68], increased wound sepsis[40,49,68,69] and faecal fistula formation[40,68,70]. None the less, as recently as 1980, peritoneal drains were used by 77 per cent of English surgeons responding to a questionnaire on prophylaxis of infection after appendicectomy[71].

In the same study[71], 56 per cent of respondents occasionally used extraperitoneal wound drains. Wound drains were associated with reduced wound-infection rates in perforated and gangrenous appendicitis in a retrospective study[72] and in one prospective trial the addition of wound drains to the use of systemic antibiotics reduced wound sepsis from 50 per cent to 21 per cent[25] but had no effect in another[73]. Several prospective studies suggest that wound drains may be harmful even when selectively used in a non-randomized fashion in patients at particular risk[2,13,24]. The evidence that wound drains prevent wound infection is not convincing, although they may prevent wound abscess formation. The only recent recommendation[74] for increased use of both wound and peritoneal drainage in acute appendicitis was based on a retrospective study of matched pairs of patients treated between 1967 and 1971 before antibiotic usage became established. Drains failed to prevent either wound or intraperitoneal abscesses, and postoperative stay was significantly longer in the drained group. Sepsis presented after drains were removed in 42·5 per cent of cases. The author suggested that the drains were removed before suppuration had time to take place and recommended that drains be left *in situ* for 10 days. Prospectively collected data now available indicate that wound infection rates much lower than those recorded in association with wound drains may be achieved without wound drains[59,62] and there is no good evidence for their continued use in contemporary practice.

Delayed closure or non-closure of the wound

The principle of delayed closure of contaminated wounds evolved in the battlefields of the First World War and was translated into civilian practice in an attempt to reduce the morbidity and mortality associated with wound sepsis after complicated appendicectomy[75]. Although widely practised in North America[47,51,76–80], the technique is not popular with British surgeons, although in some centres dissatisfaction with unacceptably high wound-sepsis rates in high-risk categories, despite appropriate antibiotics, has revived interest in this form of management.

In a retrospective review[79] of 362 children with perforated or gangrenous appendicitis from 1959 to 1968, wound sepsis developed in 76 (39·6 per cent) of 192 primarily closed wounds but in only 1 (0·6 per cent) of 164 wounds managed by delayed primary closure, although a further 6 wounds which could not be closed because of a 'purulent' appearance, were not counted as wound infections. In a similar retrospective study[80] using historical controls in a series of 83 perforated cases, delayed closure reduced wound sepsis from 34 per cent to 2·3 per cent. However, a sixfold difference in the frequency of intraperitoneal sepsis (14·6 per cent *versus* 2·3 per cent) between the two groups suggests that they were not comparable and that there were differences in other aspects of treatment, particularly in respect of antibiotic usage. In contrast, two retrospective reviews of wounds managed by delayed closure or non-closure reported incidences of wound sepsis of 15·2 per cent[81] and 31·6 per cent[82] respectively. Furthermore, the dramatic differences in the first two retrospective studies have not been confirmed in prospective studies. Delayed primary closure was associated with wound infection in 15 (26 per cent) of 58 patients compared with 20 (34 per cent) of 58 patients treated with primary closure[22]. In two studies, delayed primary closure on the fifth postoperative day was abandoned in favour of non-closure in one[48] and primary closure in the second[83] because of sepsis rates of 60 per cent and 83 per cent, respectively. In the largest prospective randomized study of 122 patients with gangrenous and perforated appendicitis, the wound-infection rate was higher (54 per cent) in the delayed primary closure group than in the two primarily closed groups (37 per cent and 17 per cent)[28]; 73 per cent of wounds left open to heal by secondary intention were 'colonized' by bacteria[48] and 77 per cent of patients with a positive culture at the time of wound closure later developed wound sepsis[28]. Such wide discrepancies in outcome may reflect differing concentrations of organisms in open wounds: when the bacterial count exceeded 10^5/g of tissue, 100 per cent wound infection resulted[84].

The most striking claim of benefit from delayed primary closure is from a prospective study of 202 patients in whom delayed closure with adhesive strips on the fifth day or later was used in every patient undergoing appendicectomy, including 46 normal appendices[85]. The authors report a zero incidence of wound infection, although they do record 19 patients in whom discharge from the wound was sufficiently troublesome to require dressings for up to 3 weeks. These patients also suffered from excessive granulation in the wound and a 'regrettable' lack of bacteriological data meant that the possibility of low-grade infection could not be excluded.

When wound sepsis rates in excess of 10 per cent persist despite appropriate antibiotics, delayed closure or non-closure of the wound proves attractive to some surgeons. Non-closure prevents wound abscesses[48] but delayed primary closure is associated with failure to close the wound because of superficial infection or later presentation of sepsis in about 10 per cent of cases[57]. There is no justification for its indiscriminate application to every grid-iron incision, regardless of operative contamination[85], when patient discomfort, increased nursing requirements and prolonged hospital stay are considered[28,85]. When delayed closure is used and quantitative bacteriological data are not available to select cases for closure, the timing of wound closure depends on clinical judgment[86] and 'the degree of purulent appearance' which may delay wound closure for up to 21 days in some patients[77]. Primary wound healing after primary wound closure may be achieved in more than 90 per cent of patients in the high-risk categories[42,59,62,87,88] and, in some centres, a policy of non-closure would imply needlessly delayed closure or non-closure for the majority of patients.

The absence of cellulitis and wound abscess is considered a satisfactory outcome after delayed closure or non-closure and is classified as a non-infected wound by most authors without comment on the lapse of time. Some of the debate on the relative merit of delayed and non-closure of wounds results from lack of definition of what constitutes infection in a wound so managed. Primarily closed wounds which discharge material containing organisms are, according to Ljungqvist's definition, classed as infected but, although this must be an almost inevitable sequel to delayed closure when some 75 per cent of wounds harbour organisms at the time of closure, the same criteria are not applied to delayed closure or non-closure.

Antibacterial agents

For practical purposes, apart from residual organisms in the skin appendages, the abdominal wall may be considered sterile when the incision is made; subsequent bacterial contamination is the result of inoculation of organisms into the layers of the wound during the operation. The need for some form of additional antibacterial agent to counter the inevitable, although variable, endogenous contamination occurring during appendicectomy is clear from contemporary reports which show a continuing incidence of in-hospital wound sepsis ranging from 5 per cent to over 30 per cent (*Table 2*) in control groups of patients. In cases of perforation or gangrene, wound sepsis develops in 11–100 per cent (mean 35 per cent) of patients in whom no active antibacterial measures are used.

Antiseptics

Historically, interest in topical antisepsis waned with the introduction of asepsis because of the toxic effects of powerful antiseptics on the exposed tissues of the operative field. There was a revival in interest with the availability of effective antiseptics of low toxicity and a few studies examined their effect alone or in combination with antibiotics. In controlled studies, noxythiolin[21,23,83,89], chlorhexidine[26,90] and hydrogen peroxide[29] did not reduce the frequency of wound infection and were ineffective in perforated and gangrenous appendicitis. Povidone-iodine spray significantly reduced overall wound infection rates (15·9–8·1 per cent) in one study[24] but not in another (28·7–29·4 per cent)[91] and had no significant effect in perforated and gangrenous appendicitis with residual wound infection rates ranging from 15·4 per cent to 62·5 per cent[24,91,92].

Two papers compared the efficacy of topical antiseptics (noxythiolin[23], chlorhexidine[26]) with topical ampicillin powder and one compared povidone-iodine with rectal metronidazole[17]. In all three papers the antibiotic was significantly more effective than the topical antiseptic, both overall and for perforated or gangrenous appendicitis. The question of combining topical antisepsis (povidone-iodine) with systemic antibiotics (metronidazole) was addressed by Galland *et al.*[93], but no benefit was found.

Antibiotics

During the last 25 years, antibiotics have been used in a bewildering variety of combinations of agents, routes and durations, in an increasing number of studies. The increased interest has resulted in a degree of standardization in design and data collection but it is still difficult to compare the results of different studies directly. The selection of cases is very variable and most prospective comparative studies specifically exclude cases with serious sepsis requiring postoperative therapeutic antibiotics, whereas others include them, although some give supplementary antibiotics. We have attempted to classify the different groups wherever possible into those given one agent or a combination of agents and have also related this to the severity of the disease.

During the last decade, since the demonstration of the important role of anaerobic organisms in post-appendicectomy wound sepsis, there has been considerable debate on appropriate prophylactic and therapeutic regimens for both low- and high-risk groups. It has been suggested that, because of the synergistic effect of aerobes and anaerobes, elimination of anaerobes with an effective agent (e.g. metronidazole) would suffice[3,4,27,31,36,38,71,91,94–98] although some would limit this to low-risk groups and would prefer a wider spectrum in high-risk groups[20,37]. The variable and often disappointing wound-sepsis rates resulting from this hypothesis have prompted the use or recommendation of either combinations of agents or an effective single agent with activity against both major groups of pathogens[6,9,13,14,32,33,35,42,43,47,49,99–102]. The majority of papers since 1980 (18 of 31) recommend both aerobic and anaerobic cover for both low- and high-risk groups although some of the best results reported have been with a single anti-anaerobic agent[31,45,97]

Topical antibiotic sprays

Aerosol sprays of a mixture of antibiotics have not been shown to reduce the incidence of postoperative wound infection[1,24,58]

Table 3 *Wound sepsis rates for topical ampicillin*

First author	Year	Low risk			High risk			Overall		
		(No.)	(WI)	(%)	(No.)	(WI)	(%)	(No.)	(WI)	(%)
Rickett[103]	69	54	1	1·9	10	1	10·0	64	2	3·1
Mountain[53]	70	55	0	0·0						
Andersen[22]	72	187	1	0·5	58	9	15·5	245	10	4·1
Mackie[23]	73	38	0	0·0	5	2	40·0	43	2	4·7
Bates[12]	74	85	1	1·2	15	2	13·3	100	3	3·0
Tanphiphat[26]	78	90	2	2·2	32	2	6·2	122	4	3·3
Chant[101]	84	33	6	18·2	18	8	44·4	51	14	27·5
Schultz[104]	83				42	15	35·7			
Pettigrew[28]	81				39	7	17·9			
Total		542	11	2·0	219	46	21·0	625	35	5·6

WI, wound infection.

The overall wound-infection rate in these three series was 29 (11·7 per cent) in 247 cases.

Ampicillin

A large dose (0·5–1 g) of topical ampicillin powder consistently reduced wound sepsis in both low- and high-risk cases in controlled trials[12,22,23,26,28,53,103]. Topical ampicillin powder as a single agent has been studied in nine papers[101,104], including the seven controlled studies mentioned, and the overall wound-infection rate was 5·6 per cent in 625 evaluable cases (*Table 3*). There were 46 (21·0 per cent) wound infections in 219 perforated or gangrenous cases and a wound-infection rate of only 2·0 per cent in low-risk cases.

Only two papers report groups of patients treated with parenteral ampicillin alone: the first with an overall wound infection rate of 1 (1·3 per cent) in 76 low-risk wounds[105] and the second with 2 (9·1 per cent) wound infections in 22 high-risk patients[97].

When ampicillin was combined with intravenous metronidazole, an overall wound-infection rate of 19 (13·4 per cent) in 142 cases[14] resulted. In perforated or gangrenous cases the rates were 13 (28·3 per cent) in 46 cases[14], 6 (12·5 per cent) in 48 cases[104] and 10 (9·4 per cent) in 106 cases[42]. A small study of 29 cases treated with pre-operative ampicillin and kanamycin gave an overall wound-infection rate of 6·9 per cent[105].

Ampicillin combined with clavulanic acid[49] or sulbactam[103] gave overall wound-sepsis rates of 13 (11·3 per cent) of 115 and 3 (8·6 per cent) of 35 cases respectively. There were 6 (21·4 per cent) wound infections in 28 high-risk cases given ampicillin and clavulanic acid compared with 8 (33·3 per cent) of 24 given metronidazole alone[49].

Metronidazole

The importance attached to anaerobic organisms in the development of postoperative wound sepsis is reflected in the widespread use of metronidazole in Europe. Comparable enthusiasm is not apparent in North America. Metronidazole, perhaps in common with other antibiotics, may delay the presentation of wound sepsis and early differences between control[18] and comparative[20] groups may be lost when follow-up is adequate.

Twenty-eight papers include groups of patients given metronidazole alone for both prophylaxis and, in some, treatment of established sepsis. In 14 papers metronidazole was given rectally pre-operatively (continued postoperatively in two[3,97]) and the overall wound-infection rate was 117 (11·0 per cent) in 1062 wounds (*Table 4a*). The wound infection rate was 6·6 per cent in low-risk patients but 25·3 per cent in perforated and gangrenous appendicitis. In 15 papers, intravenous metronidazole was given (*Table 4b*) and the corresponding rates were: overall, 16·5 per cent; low risk, 8·0 per cent; high-risk, 35·8 per cent. In two of these papers pre-operative intravenous metronidazole was supplemented with rectal metronidazole and the overall infection rate was 9 (19·1 per cent) in 47 wounds[61] and 11 (35·5 per cent) in 31 high-risk cases[98].

These average results conceal an extraordinary range in the frequency of wound sepsis: two Scandinavian studies achieved wound-infection rates of 0·8 per cent and 0·6 per cent with a single dose of rectal[31] or intravenous metronidazole[45] when perforated cases were excluded. This is in striking contrast to rates of 14·3 per cent[61] and 17·9 per cent[100] in comparable groups of patients given a single dose of intravenous metronidazole. Such high figures are interpreted[19,33,61,100] as showing the failure of metronidazole as a single prophylactic agent with exclusive anti-anaerobic activity in a situation where contamination with, and complex interactions[109] between, both aerobic and anaerobic organisms occur.

A continuing unfavourable outcome with high wound-sepsis rates is obvious in patients with perforated and gangrenous appendicitis treated with metronidazole alone. In two Scandinavian series there was a zero incidence of wound sepsis in 21 patients given pre-operative rectal metronidazole continued for 10 days postoperatively[97] and in 33 patients given a single intravenous dose of metronidazole[45], but these were patients with gangrenous appendicitis only; perforated cases were excluded or received additional antibiotics. In contrast, when a single perioperative dose only was given, the wound-sepsis rate ranged from 10 per cent[95] to 60 per cent[13]. Of the 21 evaluable papers, 14 report wound-sepsis rates in excess of 30 per cent and 5 in excess of 40 per cent. Wound-sepsis rates in the four largest series were 24 (44·4 per cent) in 54 cases[91], 22 (45·8 per cent) in 48 cases[20], 19 (48·7 per cent) in 39 cases[14] and 19 (54·3 per cent) in 35 cases[100].

The figures do not confirm a common impression that metronidazole eliminates wound sepsis as a problem after appendicectomy, particularly in perforated and gangrenous cases. However, although the frequency of wound sepsis has not been consistently reduced, there is evidence of changes in the bacteriology of subseqent wound sepsis with virtual elimination of anaerobes and a clinically significant reduction in the severity of the sepsis[3,20,95].

Twelve papers have reported the results of combinations of metronidazole with either ampicillin[14,42,104], a cephalosporin[13,16,43,87,100,102], an aminoglycoside[16,43,98], cotrimoxazole[6] or nalidixic acid[37] (*Table 5*). Patients in this relatively recent group of studies were given the drugs pre- or peroperatively and the same agents were continued postoperatively for 3–7 days if perforation was found. Four of the 12 studies concentrated exclusively on perforated and gangrenous cases[42,43,98,104]. The wound-infection rates were, overall, 50 (7·3 per cent) in 688 wounds, 60 (15·0 per cent) in 401 perforated or gangrenous cases and 16 (3·8 per cent) in 426 normal or mildly inflamed appendices.

No single combination of agent with metronidazole was clearly superior and in the perforated and gangrenous groups the lowest rates in series of more than 20 cases were with cephaloridine (IV and by topical lavage, 3·8 per cent[87]), nalidixic

Table 4 *Wound sepsis rates for metronidazole*
(*a*) *Rectal metronidazole*

		Low risk			High risk			Overall		
First author	Year	(No.)	(WI)	(%)	(No.)	(WI)	(%)	(No.)	(WI)	(%)
Willis[3]	76							49	5	10·2
Rodgers[94]	79							42	2	4·8
Salem[17]	79	55	1	1·8	10	3	30·0	65	4	6·2
Ford[96]	80	34	0	0·0	5	1	20·0	39	1	2·6
Pinto[106]	80	96	5	5·2	31	5	16·1	127	10	7·9
Bates[18]	80	70	11	15·7	22	7	31·8	92	18	19·6
Tanner[95]	80	44	0	0·0	10	1	10·0	54	1	1·9
Morris[13]	80	57	8	14·0	10	6	60·0	67	14	20·9
Foster[91]	81	206	19	9·2	54	24	44·4	260	43	16·5
Roland[97]	81				21	0	0·0			
Kortelainen[31]	82	97	0	0·0	27	1	3·7	124	1	0·8
Hutchinson[32]	83							67	11	16·4
Chiam[6]	83							76	7	9·2
O'Rourke[107]	84	53	3	5·7						
Total		712	47	6·6	190	48	25·3	1062	117	11·0
(*b*) *Intravenous metronidazole*										
Greenall[108]	79							49	1	2·0
Gottrup[45]	80	134	1	0·7	31	0	0·0*	167	1	0·6
Paakonen[19]	82	58	2	3·4						
Galland[93]	83	157	12	7·6	43	15	34·9	200	27	13·5
Flannigan[98]†	83				31	11	35·5			
Keiser[33]	83	24	1	4·2	6	2	33·3	30	3	10·0
Corder[20]	83				48	22	45·8			
Lau[14]	83a	102	14	13·7	39	19	48·7	141	33	23·4
Lau[100]	83b	67	12	17·9	35	19	54·3	102	31	30·4
Ambrose[46]	83	73	3	4·1	25	6	24·0	98	9	9·2
Chant[101]	84	38	2	5·3	19	6	31·6	57	8	14·0
Buckels[61]†	85	35	5	14·3	12	4	33·3	47	9	19·1
Drumm[49]	85	92	13	14·1	24	8	33·3	116	21	18·1
Kling[37]	85	50	0	0	–	–	–	–	–	–
El-Sefi[16]	86	86	8	9·3	14	5	35·7	100	13	13·0
Total		916	73	8·0	327	117	35·8	1107	156	14·1
Overall		1628	120	7·4	517	165	31·9	2169	273	12·6

* Gangrenous cases only; additional antibiotics used for perforated cases; †IV and rectal metronidazole used. WI, wound infection

Table 5 *Wound sepsis rates for metronidazole in combination with other antibiotics*

			Low risk			High risk			Overall		
First author	Year	Additional agent	(No.)	(WI)	(%)	(No.)	(WI)	(%)	(No.)	(WI)	(%)
Morris[13]	80	cefazolin	61	2	3·3	6	0	0·0	67	2	3·0
Lau[14]	83	ampicillin	96	6	6·3	46	13	28·3	142	19	13·4
Saario[43]	83	gentamicin				23	4	17·4			
Saario[43]	83	cefuroxime				23	4	17·4			
Flannigan[98]	83	gentamicin				28	8	28·6			
Lau[100]	83b	cefotaxime	61	4	6·6	42	10	23·8	103	14	13·6
Schultz[104]	83	ampicillin				48	6	12·5			
Chiam[6]	83	cotrimoxazole							73	2	2·7
Danish MC[42]	84	ampicillin				106	10	9·4			
Orr[87]	84	cephaloridine	39	0	0·0	26	1	3·8	65	1	1·5
Kling[37]	85	nalidixic acid				22	1	4·5			
El-Sefi[16]	86	cefazolin	87	2	2·3	13	2	15·4	100	4	4·0
El-Sefi[16]	86	tobramycin	82	2	2·4	18	1	5·6	100	3	3·0
Foster[102]	86	cefotaxime							38	5	13·2
Total			426	16	3·8	401	60	15·0	688	50	7·3

WI, wound infection

acid (4·5 per cent)[37] and ampicillin (14·5 per cent)[14,42,104]. The combinations of metronidazole with cefuroxime[43], cefotaxime[100] or cefazolin[16] gave wound-infection rates of 17·4 per cent, 23·8 per cent and 15·4 per cent respectively. For metronidazole in combination with an aminoglycoside, wound sepsis developed in a total of 13 (18·8 per cent) of 69 wounds[16,43,98].

Cephalosporins

A variety of cephalosporins has been used either for their activity against aerobes alone, in combination with an anti-anaerobic agent, or as a single agent with activity against both major groups of pathogens (*Table 6*).

When used alone, 'first'- and 'second'-generation cephalosporins, cephaloridine[25,110] and cefamandole[30,34,111], with no significant antianaerobic activity, reduced wound sepsis compared with controls not given antibiotics. Wound-sepsis rates were: overall, 19 (13·4 per cent) in 142; low risk, 2 (1·0 per cent) in 207; high risk, 29 (29·3 per cent) in 99 patients. For 'third'-generation cephalosporins and cephamycins, cefazolin[13],

Table 6 *Wound sepsis rates for cephalosporins*

			Low risk			High risk			Overall		
First author	Year	Antibiotic	(No.)	(WI)	(%)	(No.)	(WI)	(%)	(No.)	(WI)	(%)
Everson[25]	77	cephaloridine	70	0	0·0	30	9	30·0	100	9	9·0
Foster[110]	78	cephaloridine	70	1	1·4						
Morris[13]	80	cefazolin	60	6	10·0	11	8	72·7	71	14	19·7
Bussitil[30]	81	cefamandole	46	1	2·2						
Berne[111]	82a	cefamandole				48	10	20·8			
Berne[111]	82a	cefoperazone				42	7	16·7			
Gledhill[34]	83	cefamandole	21	0	0·0	21	10	47·6	42	10	23·8
Lau[100]	83	cefotaxime	65	4	6·2	38	9	23·7	103	13	12·6
Corder[20]	83	cefoxitin				49	20	40·8			
Winslow[35]	83	cefoxitin	51	0	0·0						
Danish MC[42]	84	cefoxitin				103	10	9·7			
O'Rourke[107]	84	cefoxitin	58	3	5·2						
Lau[9]	85	cefotaxime	212	6	2·8	77	18	23·4	289	24	8·3
Lau[9]	85	cefoperazone	207	4	1·9	78	16	20·5	285	20	7·0
Lau[9]	85	latamoxef	215	7	3·3	75	6	8·0	290	13	4·5
Buckels[61]	85	cefotetan	47	2	4·3						
Garcia[112]	86	cefmetazole	36	0	0·0	9	0	0·0	45	0	0·0
Total			1158	34	2·9	581	123	21·2	1225	103	8·4

WI, wound infection

cefoperazone[9,111], cefotaxime[9,100], cefoxitin[20,35,42], latamoxef[9], cefmetazole[112] and cefotetan[61], combined wound-infection rates were: overall, 84 (7·8 per cent) in 1083; low risk, 32 (3·4 per cent) in 941 and high risk, 94 (19·5 per cent) in 482 patients.

There were no wound infections in 45 low-risk patients given cefamandole and carbenicillin[30] and when cefotaxime[100] and cefazolin[13,16] were combined with metronidazole there were 8 (3·8 per cent) in 209 similar low-risk patients. The wound-infection rate was 16 (19·0 per cent) in 84 high-risk patients treated with cefuroxime[43], cefotaxime[100,102] or cefazolin[13] in combination with metronidazole. The overall wound-infection rate for a cephalosporin combined with an anti-anaerobic agent was 25 (7·1 per cent) in 353 cases.

Tetracycline

Although tetracycline is no longer considered an agent of first choice because of the level of resistance among both aerobic and anaerobic pathogens at concentrations achieved in conventional therapy, there is evidence from a comparative clinical trial, in colonic surgery, of prophylactic benefit from peroperative topical lavage[113] with tetracycline in a concentration of 1000 mg/litre. This supports earlier studies of tetracycline lavage in appendicitis in which overall wound-sepsis rates were reduced from 18 per cent to 2 per cent[1] and 23 per cent to 7 per cent[114]. Retrospective analysis of perforated appendicitis in childhood suggested a similar advantage for tetracycline lavage over noxythiolin[115] and in our own experience, a prospective study over 10 years[88] shows a low wound-sepsis rate with an antibiotic policy based on peroperative tetracycline lavage. Since 1983 we have supplemented tetracycline lavage in high-risk cases with a single dose of intravenous metronidazole in gangrenous or perforated cases with localized sepsis or with a 3-day course of metronidazole, gentamicin and ampicillin in patients with diffuse peritonitis. There was a statistically insignificant reduction in wound sepsis following this change in practice and the wound-infection rates during the ten years were: overall, 17 (3·7 per cent) in 456; low risk, 8 (2·4 per cent) in 339; high risk, 9 (7·7 per cent) in 117 patients[88].

Aminoglycosides

Only one study has examined an aminoglycoside as the sole therapeutic agent in high-risk patients[39] and noted 10 (71·4 per cent) wound infections in 14 patients. Gentamicin has been used in combination with clindamycin[47,50,92,111], metronidazole[43,98] and tobramycin with metronidazole[16]. Only in El-Sefi's study[16] has an aminoglycoside and metronidazole been used as a prophylactic regimen in 82 low-risk patients with 2 (2·4 per cent) wound infections. All the other studies were in high-risk patients and there were 15 (13·8 per cent) wound infections in 109 primarily closed wounds[16,43,92,98].

Discussion

The frequency of wound sepsis after appendicectomy depends on the severity of the inflammatory process and the degree of contamination of the abdominal parietes at operation. Protection of the wound, usually with antiseptic-soaked packs, is recommended by several authors but is of no proven benefit although it has a logical and aesthetic appeal. The major issues, however, are the use of drains, prophylactic antibiotics in low- and high-risk groups and delayed closure or non-closure of the wound.

Wound drains may be dismissed in that there is no convincing evidence of benefit, they may increase the frequency of sepsis and, if they are to be relied upon to prevent wound abscess formation, must be retained *in situ* for 10 days

The role of antibiotics is much more complex. At least two studies with only small and statistically insignificant reductions in wound sepsis after an antibiotic (metronidazole)[19,106] suggest that prophylactic antibiotics are unnecessary in low-risk patients and that concentration on the technical aspects of the procedure is more important[19]. This is a minority view, however, and antibiotics are generally considered appropriate for both low- and high-risk patients.

Low risk

Wound sepsis should be infrequent in low-risk patients undergoing appendicectomy and infection rates of less than 5 per cent have been reported without prophylactic antibiotics[26,38], although the average figure is 10 per cent (*Table 2*). The efficacy of prophylactic antibiotics is related to the severity of contamination[93] and a variety of prophylactic antibiotic regimens have proved effective in low-risk cases. It is difficult to demonstrate clear superiority of one regimen over another.

In studies of prophylactic antibiotics, wound-infection rates of less than 2 per cent have been reported in 14 papers with at least 50 patients. In four papers the follow-up data[12,25,116] or the definition of wound sepsis[22] are inadequate and in three a postal questionnaire[36,38,45] was used. There were no wound infections after 50 and 97 low-risk appendicectomies after a single intravenous[37] or rectal[31] dose of metronidazole. There

Table 7 *Summary of publications with more than 50 high-risk cases and wound-sepsis rate less than 10 per cent*

First author	Year	Antibiotics	Route of administration	Cases (No.)	(WI)	(%)	
Gottrup[45]	80	metronidazole +pen/strep	PR+IV Topical*+IV	66	0	0·0	5 days for peritonitis
Eklund[38]	87	tinidazole	Topical†	51	1	2·0	
MacKellar[59]	86	metronidazole gent/amp or cefamandole	PR IV IV	158	5	3·2	5 days for peritonitis
Krukowski[88]	88	tetracycline +metronidazole +amp/gent	Topical IV IV	117	9	7·7	3 days for peritonitis
Lau[9]	85	latamoxef	IV	75	6	8·0	5 days for peritonitis
Danish MC[42]	84	metronidazole +amp	IV IV	106	10	9·4	5 days for peritonitis
Danish MC[42]	84	cefoxitin	IV	103	10	9·7	5 days for peritonitis
Total				676	41	6·1	

* Penicillin/streptomycin lavage in perforated cases only; †gangrenous cases only; peritonitis excluded. WI, wound infection; PR, per rectum; IV, intravenous administration; pen, penicillin; strep, streptomycin; gent, gentamicin; amp, ampicillin

was one wound infection after 55 operations with a single dose of rectal metronidazole[17]. Similar sepsis rates have been reported with topical agents, such as ampicillin powder (1·9 per cent)[103], chlorhexidine (1·4 per cent)[90], polyantibiotic spray[24] or povidone-iodine spray (1·6 per cent)[24]. Wound-sepsis rates of 1·4 per cent and 1·9 per cent were achieved with three intravenous doses of ticarcillin[46] and a single dose of intravenous cefoperazone[9].

There is good evidence that prophylactic antibiotics reduce the frequency of wound sepsis in low-risk patients and that a single pre- or peroperative dose should suffice. In low-risk cases the need for antibacterial activity against both aerobic and anaerobic organisms is uncertain. Although low sepsis rates with a single dose of metronidazole have been reported[17,31,33], the average figure is much higher at over 7 per cent (*Table 4*) and it seems logical to use a single broad-spectrum agent. In our own practice, topical tetracycline lavage supplemented with an intravenous dose of the same agent resulted in 8 (2·4 per cent) wound infections in 339 low-risk patients[88]. Acceptably low rates have also been reported with second- and third-generation cephalosporins.

High risk

The situation in high-risk cases is complicated by the variable risk within this category. Gangrenous or perforated appendicitis with localized sepsis carries a risk of wound sepsis similar to that of perforated appendicitis with diffuse peritonitis, but the difference in severity of the disease is such that, although antibiotic administration may be successfully reduced to a very short course or even a single dose in the former, a therapeutic course of antibiotics is required for 3–7 days in the latter. Many published studies exclude patients with diffuse peritonitis given therapeutic antibiotics and it is possible that the true frequency of wound sepsis is higher than reported.

In addition, although variability in wound sepsis rates for similar antibiotics may be explicable on the basis of small study sizes and chance variation, it is probable that differences in the conduct of the operation are relevant. The ability of appropriate antibiotics to modify the inflammatory response in acute appendicitis is beyond question but the benefit may be masked by traumatic surgery and avoidable contamination of the wound.

Considering first the results with wounds closed primarily, only two papers[36,38] report a sufficient number (more than 50) of high-risk patients not given antibiotics, one of which studies[36] used a postal follow-up and in one[38], patients with severe sepsis were excluded. The resulting wound-sepsis rates were respectively 28·8 per cent[36] and 13·8 per cent[38] and are lower than reported in many studies using antibiotics.

When the six studies which included more than 50 high-risk cases and reported wound-sepsis rates of less than 10 per cent are considered, the effect of combined activity against both aerobic and anaerobic organisms is clearer (*Table* 7). Gottrup[45] reported no wound infections in 66 cases but only the 31 patients with gangrenous appendicitis were given no more than a single intravenous dose of metronidazole. The remaining 35 patients with perforation had additional topical and parenteral penicillin and streptomycin. Similarly, the excellent results reported by Eklund[38], of only one wound infection in 51 cases, refers only to gangrenous appendicitis; patients with perforation were excluded from this study of peroperative topical tinidazole. The adequacy of follow-up in both these studies is also open to criticism because of their reliance on a postal questionnaire. The results with metronidazole alone have otherwise been disappointing and activity against both aerobic and anaerobic organisms as used in the other four studies appears necessary. The paper by MacKellar and Mackay[59] is noteworthy in that it reports the excellent results of a consistent policy for the management of children with appendicitis. There were only 5 (3·2 per cent) wound infections in 158 cases. High-risk cases were given metronidazole in combination with either gentamicin and ampicillin or cefamandole, supplemented with either saline or povidone-iodine peritoneal lavage. All the above studies with wound-sepsis rates of less than 10 per cent in high-risk cases have used antibiotics active against both aerobic and anaerobic organisms and in two a single agent, cefoxitin or latamoxef, was effective. Topical antibiotic lavage was a feature of three of these reports[38,45,88] and supports the experimental finding that topical antibiotic lavage is an effective and economical treatment which reduces the requirement for postoperative therapeutic antibiotics[117]. Acceptably low wound-sepsis rates in perforated appendicitis may be achieved with careful technique, primary wound closure and effective antibiotics.

In some centres and particularly in North America, however, despite systemic antibiotics the frequency of wound sepsis in high-risk cases has been disappointingly high and has led to the adoption of delayed primary closure of the wound. Although such management prevents suppuration within a closed space in the wound and reduces morbidity due to spreading sepsis, this type of serious wound infection is now a rarity when appropriate antibiotics are used[118]. Delayed closure results in failure to close the wound within 5–7 days in a substantial number of cases and the disadvantages of patient discomfort and increased nursing care make the method unattractive when low wound-sepsis rates may be achieved with primary closure and appropriate antibiotics.

In conclusion, we recommend that in low-risk cases antibiotics should be restricted to a single pre- or peroperative dose of a broad-spectrum agent effective against both aerobic and anaerobic organisms. Peroperative antibiotic lavage is associated with some of the lowest wound-sepsis rates in both low- and high-risk cases and is an attractively simple routine in all cases. Although we have classified gangrenous appendicitis as 'high risk', it is clear that uncomplicated gangrenous appendicitis may be successfully managed in similar fashion. Only when perforation with established diffuse sepsis is present are systemic antibiotics for 3–5 days necessary. Despite the good results reported in small series with antibiotics active against only anaerobic organisms, a broad spectrum of activity with either a single antibiotic or a combination of agents appears preferable both as treatment for the peritonitis and as prophylaxis against wound sepsis. There is little convincing evidence that newer and often more expensive agents offer significant advantages over established antibiotics. When necessary, we continue to rely on the triple regimen of gentamicin, ampicillin and metronidazole as a supplement to peroperative antibiotic lavage. When these measures are allied to sound surgical technique, wound infection should be less than 3 per cent in low-risk cases and less than 10 per cent in high-risk cases. On the evidence presented we consider non-closure of the wound to be an unnecessary measure in acute appendicitis.

References

1 Longland CJ, Gray JG, Lees W, Garrett JAM. The prevention of infection in appendicectomy wounds. *Br J Surg* 1971; **58**: 117–9.

2 Gilmore OJA, Martin TDM, Fletcher BN Prevention of wound infection after appendicectomy. *Lancet* 1973; **i**: 220–2.

3. Willis AT, Ferguson IR, Jones PH *et al.* Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br Med J* 1976; **i**: 318–21.

4. Leigh OA, Pease R, Henderson H, Simmons K, Russ R Prophylactic lincomycin in the prevention of wound infection following appendicectomy: a double blind study. *Br J Surg* 1976; **63**: 973–7.

5. Cruse PJE, Foord R. The epidemiology of wound infection. A 10-year prospective study of 62,939 wounds. *Surg Clin North Am* 1980; **60**: 27–40.

6. Chiam HL, Chee CP, Chea KC, Somasundaram K, Puthucheary SD. The prevention of postappendicectomy sepsis by metronidazole and cotrimoxazole. a controlled double blind trial. *Aust NZ J Surg* 1983; **53**: 421–5.

7. Russell I. Clinical trials and evaluation of surgical procedures. *Surgery (Oxford)* 1984; **1**. 196–9.

8. Evans M. Pollock AV Trials on trial. A review of trials of antibiotic prophylaxis. *Arch Surg* 1984; **119**: 109–13.

9. Lau W-Y, Fan S-T, Chu K-W, Suen H-C, Yiu T-F, Wonf K-K. Randomised, prospective, and double-blind trial of new β-lactams in the treatment of appendicitis. *Antimicrob Agents Chemother* 1985; **28**: 639–42

10. Ljungquist V. Wound sepsis after clean operations. *Lancet* 1965; **i**: 1095–7.

11. Cruse PJE, Foord R. A five-year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; **107**: 206–10.

12 Bates T, Down RHL, Houghton MCV, Lloyd GL. Topical ampicillin in the prevention of wound infection after appendicectomy. *Br J Surg* 1974; **61**: 489–92.

13 Morris WT, Innes DB, Richardson RA, Lee AJ, Ellis-Pegler RB. The prevention of post-appendicectomy sepsis by metronidazole and cephazolin: a controlled double blind trial. *Aust NZ J Surg* 1980; **50**: 429–33.

14. Lau WY, Fan ST, Yiu TF, Wong SH. Prophylaxis of post-appendicectomy sepsis by metronidazole and ampicillin: a randomised, prospective and double blind trial. *Br J Surg* 1983, **70**: 155–7.

15. Krukowski ZH, Stewart MPM, Al-Sayer HM, Matheson NA. Infection after abdominal surgery. five year prospective study. *Br Med J* 1984; **288**: 278–80.

16. El-Sefi TA, El-Wadi HM, Shehata MI, Al-Hindi MA. The place of antibiotics in the prevention of post-appendicectomy sepsis: a prospective study of 400 cases. *Int Surg* 1986; **71**: 18–21.

17 Salem RJ, Johnson J, Devitt P. Short term metronidazole therapy contrasted with povidone-iodine spray in the prevention of wound infection after appendicectomy. *Br J Surg* 1979; **66**: 430–1.

18. Bates T, Touquet VLR, Tutton MK, Mahmoud SE, Reuther JWA Prophylactic metronidazole in appendicectomy: a controlled trial. *Br J Surg* 1980; **67**: 547–50.

19. Paakonen M, Mononen P, Kostianen S. The value of a single intravenous dose of metronidazole as prophylaxis against wound infection after appendicectomy. *Ann Chirurg Gynaecol* 1982; **71**: 137–9.

20. Corder AP, Prior JE, Bates T, Harrison M, Donaldson PJ Metronidazole versus cefoxitin in severe appendicitis—a trial to compare a single intraoperative dose of two antibiotics given intravenously *Postgrad Med J* 1983; **59**: 720–3.

21. Bird GG, Bunch GA, Croft CB *et al.* Topical noxythiolin antisepsis: report of a controlled trial *Br J Surg* 1971; **58**: 447–8.

22. Andersen B, Bendtsen A, Holbraad L, Schantz A. Wound infections after appendicectomy. *Acta Chir Scand* 1972; **138**: 531–6.

23. Mackie B, Shafi MS, Grundy DJ, Ralph DNL, Haynes S Topical ampicillin and noxythiolin antisepsis in appendicectomy wounds. *Br J Clin Pract* 1973; **27**: 57–61.

24. Gilmore OJA, Martin TDM. Aetiology and prevention of wound infection in appendicectomy. *Br J Surg* 1974; **61**: 281–7.

25. Everson NW, Fossard DP, Nash JR, Macdonald RC Wound infection following appendicectomy: the effect of extraperitoneal wound drainage and systemic antibiotic prophylaxis *Br J Surg* 1977; **64**: 236–8.

26. Tanphiphat C, Sangsubhan C, Vongvaravipatr V *et al.* Wound infection in emergency appendicectomy: a prospective trial with topical ampicillin and antiseptic solution irrigation. *Br J Surg* 1978; **65**. 89–91.

27. Donovan IA, Ellis D, Gatehouse D *et al.* One-dose antibiotic prophylaxis against wound infection after appendicectomy a randomized trial of clindamycin, cefazolin sodium and a placebo. *Br J Surg* 1979; **66**. 193–6.

28. Pettigrew RA. Delayed primary wound closure in gangrenous and perforated appendicitis. *Br J Surg* 1981; **68**: 635–8.

29. Lau WY, Wong SH. Randomized, prospective trial of topical hydrogen peroxide in appendectomy wound infection High risk factors *Am J Surg* 1981; **142** 393–7.

30. Busittil RW, Davidson RK, Fine M, Tomkins RK Effect of prophylactic antibiotics in acute non-perforated appendicitis. A prospective, randomised double blind clinical study *Ann Surg* 1981; **194**: 502–9.

31. Kortelainen P, Huttunen R, Kairaluoma MI, Mokka RE, Laitinen S, Larmi TKI. Single dose intra-rectal metronidazole prophylaxis against wound infection after appendicectomy. *Am J Surg* 1982, **143**: 244–5.

32. Hutchinson GH, Patel BG, Doig CM A double-blind controlled trial of metronidazole suppositories in children undergoing appendicectomy. *Curr Med Res Opin* 1983; **8**: 441–5.

33. Keiser TA, McKenzie RL, Feld R, Leers N. Prophylactic metronidazole in appendectomy: a double blind controlled trial. *Surgery* 1983; **93**: 201–3.

34. Gledhill T, Odurny A, Weaver PC. A controlled trial of single dosage cefamandole in the prophylaxis of wound infections in appendectomy. *Surg Gynecol Obstet* 1983, **156**. 295–6

35. Winslow LE, Dean RE, Harley JW. Acute nonperforating appendicitis *Arch Surg* 1983; **118**: 651–5.

36. Viitanen J, Tunturi T, Auvinen O, Pessi T. Tinidazole prophylaxis in appendicectomies. *Scand J Gastroenterol* 1984; **19**: 111–15

37. Kling P-A, Holmlund D, Burman LG. Prevention of postoperative infection in appendicectomy by single dose intravenous metronidazole. *Acta Chir Scand* 1985, **151**: 73–6.

38. Eklund A-E, Tunevall TG. Prevention of postoperative wound infection after appendectomy by local application of tinidazole: A double-blind study. *World J Surg* 1987; **11**: 263–6

39. Raahave D, Poulson PE. Perforated appendicitis and antibiotics: A survey and a controlled clinical trial. *Acta Chir Scand* 1970; **136**: 715–23.

40. Stone HH, Hooper CA, Millikan WJ. Abdominal drainage following appendectomy and cholecystectomy. *Ann Surg* 1978, **187**: 606–12

41. Kelly MJ. Wound infection: a controlled clinical and experimental demonstration of synergy between aerobic (*Escherichia coli*) and anaerobic (*Bacteroides fragilis*) bacteria. *Ann R Coll Surg Engl* 1980; **62**: 52–9

42. Danish Multicenter Study Group. A Danish multicenter study:

cefoxitin versus ampicillin + metronidazole in perforated appendicitis *Br J Surg* 1984; **71**: 144–6.

43. Saario I, Arvilommi H, Silvola H. Comparison of cefuroxime and gentamicin in combination with metronidazole in the treatment of peritonitis due to perforation of the appendix. *Acta Chir Scand* 1983; **149**: 423–6

44. Krukowski ZH, Al-Sayer HM, Reid TMS, Matheson NA. Effect of topical and systemic antibiotics on bacterial growth kinesis in generalized peritonitis in man. *Br J Surg* 1987; **74**: 303–6.

45. Gottrup F. Prophylactic metronidazole in prevention of infection after appendicectomy: report of a double-blind trial. *Acta Chir Scand* 1980; **146**. 133–6.

46. Ambrose NS, Donovan IA, Wise R, Lowe P. Metronidazole and ticarcillin in the prevention of sepsis after appendicectomy. *Am J Surg* 1983, **140**: 346–8.

47. Berne TV, Appleman MD, Chenella FC, Yellin AE, Gill MA, Heseltine PNR. Surgically treated gangrenous or perforated appendicitis. A comparison of aztreonam and clindamycin versus gentamicin and clindamycin. *Ann Surg* 1987; **205**: 133–7.

48. Brennan SS, Smith GMR, Evans M, Pollock AV The management of the perforated appendix: a controlled clinical trial. *Br J Surg* 1982; **69**: 510–2.

49. Drumm J, Donovan IA, Wise R, Lowe P. Metronidazole and augmentin in the prevention of sepsis after appendicectomy. *Br J Surg* 1985; **72**: 571–3.

50. Heseltine PNR, Yellin AE, Appleman MD *et al.* Imipenem therapy for perforated and gangrenous appendicitis *Surg Gynecol Obstet* 1986; **162**: 43–8.

51. Yellin AE, Heseltine PNR, Berne TV *et al.* The role of pseudonomas species in patients treated with ampicillin and sulbactam for gangrenous and perforated appendicitis. *Surg Gynecol Obstet* 1985, **161**: 303–7

52. Jones PF. *Abdominal emergencies in infancy and childhood. Emergency Abdominal Surgery*, 2nd ed. Oxford · Blackwell, 1987; 22–4.

53. Mountain JC, Seal PV. Topical ampicillin in grid-iron appendicectomy wounds. *Br J Clin Pract* 1970; **24**: 111–5.

54. Gilbert SR, Emmens RW, Putman TC. Appendicitis in children *Surg Gynecol Obstet* 1985; **161**: 261–5.

55. Russell RCG. Surgical technique. *Br J Surg* 1987; **74**: 763–4.

56. Pettigrew RA, Burns HJG, Carter DC. Evaluating surgical risk · the importance of technical factors in determining outcome. *Br J Surg* 1987; **74** · 791–4.

57. Gaffney PR. Wound infection in appendicitis: effective prophylaxis. *World J Surg* 1984; **8**: 287–92.

58. Stoller JL. Topical antibiotic therapy in acute appendicitis. *Br J Clin Pract* 1965; **19**. 687–8.

59. MacKellar A, Mackay AJ. Wound and intraperitoneal infection following appendicectomy for perforated or gangrenous appendicitis. *Aust NZ J Surg* 1986, **56**: 489–91.

60. Krukowski ZH, Matheson NA. The management of peritoneal and parietal contamination in abdominal surgery. *Br J Surg* 1983; **70**: 440–1.

61. Buckels JAC, Brookstein R, Boser R, Bullen B, Alexander-Williams J. A comparison of the prophylactic value of cefotetan and metronidazole in appendectomy. *World J Surg* 1985; **9**. 814–8.

62. Krukowski ZH, Koruth NM, Matheson NA. Antibiotic lavage in emergency surgery for peritoneal sepsis. *J R Coll Surg Edinb* 1986; **31**: 1–6.

63. Raahave D. Effect of plastic skin and wound drapes on the density of bacteria in operation wounds. *Br J Surg* 1976; **63**: 421–6.

64. Watters DAK, Walker WA, Abernethy BC. The appendix stump should it be inverted? *Ann R Coll Surg Engl* 1984; **66**: 92–3.

65. Engstrom L, Fenyo G. Appendicectomy: assessment of stump invagination versus simple ligation: a prospective, randomised trial. *Br J Surg* 1985; **72**: 971–2.

66 Foster GE, Hardy EG, Hardcastle JD. Subcuticular suturing after appendicectomy *Lancet* 1977; **i**: 1128–9.

67 Yates JL. An experimental study of the local effects of peritoneal drainage. *Surg Gynecol Obstet* 1905; **1**: 473–92

68. Magarey CJ, Rickford CRK, Chant ADB, Magarey JR. Peritoneal drainage and systemic antibiotics after appendicectomy: A prospective trial. *Lancet* 1971; **ii**: 179–82.

69. Leigh DA, Simmons K, Norman E. Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J Clin Pathol* 1974; **27**: 997–1000.

70 Greenall MJ, Evans M, Pollock AV. Should you drain a perforated appendix? *Br J Surg* 1978, **85**: 880–2.

71 Campbell WB. Prophylaxis of infection after appendicectomy: a survey of current surgical practice. *Br Med J* 1980; **281**: 1597–600.

72. Vinnicombe J. Appendicectomy wound infection, drainage, and antibiotics *Br J Surg* 1964; **51**: 328–31.

73. Farrar DJ, Maybury NK, Sanson JR. The use of closed wound suction drainage after appendicectomy. *Br J Clin Pract* 1973; **27**: 63–5.

74 Isbister WH. Appendicectomy drains: a case controlled study. *NZ Med J* 1983; **96** · 1005–7.

75. Wilkie DPD. Observations on mortality in acute appendicular disease. *Br Med J* 1931; **i**: 253–5.

76. Edlich RF, Rogers W, Kaspar G, Kaufman D, Tsung MS, Wangensteen O. Studies in the management of the contaminated wound. *Am J Surg* 1969; **117** · 323–9

77. Mervine TB. The handling of contaminated wounds. *Surg Clin North Am* 1973; **53**: 611–5.

78. Maddox JR, Johnson WW, Sergeant CK. Appendectomies in a children's hospital A five-year survey *Arch Surg* 1964; **89**: 223–5.

79. Stone HH, Saunders SL, Martin JD. Perforated appendicitis in children. *Surgery* 1972; **69** · 673–9.

80. Grosfeld JL, Solit RW. Prevention of wound infection in perforated appendicitis · experience with delayed primary closure. *Ann Surg* 1968; **168**. 891–5.

81 Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis. A critical review of diagnosis and treatment in 1,000 cases. *Arch Surg* 1975; **110**: 674–84

82. Pieper R, Forsell P, Kager Lars. Perforating appendicitis A nine year survey of treatment and results. *Acta Chir Scand* 1986 (suppl).

83. Fraser-Moodie A. Prevention of wound infections after appendicectomy. *J R Coll Surg Edinb* 1974; **19**: 121–3.

84. Krizek TJ, Robson MC. The evolution of quantitative bacteriology in wound management. *Am J Surg* 1975; **130**: 579–84.

85. Gray DWR, Brabham RF, Kay S, Lowdon IMR, Thomson H. The role of prophylactic antibiotics in appendectomy using delayed primary closure. *Surg Gynecol Obstet* 1983; **156**: 323–5

86. Hunt TK, Knighton DR, Goodson WH. Wound healing. In · *Current Surgical Diagnosis and Treatment*, 7th ed. Lange: Los Altos, 1985; 97

87. Orr JD. Antibiotic peritoneal lavage in childhood appendicitis. *J R Coll Surg Edinb* 1984; **29**: 307–9.

88. Krukowski ZH, Matheson NA A ten-year computerized audit of infection after abdominal surgery. *Br J Surg*, in press

89. Gurry JF, King DW, Rutter KP, Brooke BN. A controlled trial of intraperitoneal noxytiolin in perforated appendicitis. *Br J Surg* 1976; **63**: 400–1

90. Crosfill M, Hall R, London D. The use of Chlorhexidine antisepsis in contaminated surgical wounds *Br J Surg* 1969; **56**: 906–8.

91. Foster GE, Bolwell J, Balfour TW *et al.* Clinical and economic consequences of wound sepsis after appendicectomy and their modification by metronidazole or povidone iodine. *Lancet* 1981; **i**: 769–771.

92 Sherlock DJ, Ward A, Holl-Allen RTJ. Combined preoperative antibiotic therapy and intraoperative povidone-iodine. *Arch Surg* 1984; **119** · 909–11.

93 Galland RB, Karlowski T, Midwood CJ, Madden MV, Carmalt H Topical antiseptics in addition to peroperative antibiotics in preventing post-appendicectomy wound infections. *Ann R Coll Surg Engl* 1983, **65** · 397–9

94. Rodgers J, Ross D, McNaught W, Gillespie G. Intrarectal metronidazole in the prevention of anaerobic infections after emergency appendicectomy · a controlled clinical trial. *Br J Surg* 1979; **66**: 425–7.

95. Tanner WA, Ali AE, Collins PG, Fahy AM, Lane BE, McCormack T. Single dose intra-rectal metronidazole as prophylaxis against wound infection following emergency appendicectomy. *Br J Surg* 1980; **67** · 809–10.

96. Ford WDA, MacKellar A, Richardson CJL. Pre- and postoperative rectal metronidazole for the prevention of wound infection in childhood appendicitis *J Pediatr Surg* 1980; **15**: 160–3.

97. Roland M, Bergan T, Jakobsen A, Liavag I. Effect of metronidazole and ampicillin on patients with gangrenous or perforated appendicitis. A comparative study. *Scand J Infect Dis* 1981 (Suppl 26): 92–5.

98 Flannigan GM, Clifford RP, Carver RA, Yule AG, Madden NP Antibiotic prophylaxis in acute appendicitis. *Surg Gynecol Obstet* 1983, **150**. 209–11.

99. Okubadejo OA, Peet TND, Turner DTL Clindamycin prophylaxis in appendicectomy wound infections. In: Williams JD, Geddes AM, eds. *Chemotherapy, Vol. 1*. New York· Plenum Press, 1976. 287–93.

100. Lau WY, Fan ST, Yiu TF, Poon GP, Wong SH. Prophylaxis of postappendicectomy sepsis by metronidazole and cefotaxime, a randomized, prospective and double blind trial. *Br J Surg* 1983, **70**: 670–2.

101. Chant ADB, Turner DTL, Machin D. Metronidazole v ampicillin: differing effects on the postoperative recovery. *Ann R Coll Surg Engl* 1984; **66**· 96–7

102 Foster MC, Kapila L, Morris DL, Slack RCB. A randomized comparative study of sulbactam plus ampicillin vs. metronidazole plus cefotaxime in the management of acute appendicitis in children. *Rev Infect Dis* 1986; **8**: (suppl 5): 634–8.

103. Rickett JWS, Jackson BT. Topical ampicillin in the appendicectomy wound: report of double-blind trial. *Br Med J* 1969, **4**: 206–7.

104. Schultz A, Jorgensen PM, Jorgensen SP. Septic complications after appendicectomy for perforated appendicitis. A controlled clinical trial of metronidazole and topical ampicillin *Acta Chir Scand* 1983; **149**· 517–20.

105. Wright JE. Appendicitis in childhood. reduction in wound infection with pre-operative antibiotics *Aust NZ J Surg* 1982; **52**: 127–9

106. Pinto DJ, Sanderson PJ. Rational use of antibiotic therapy after appendicectomy. *Br Med J* 1980; **280**: 275–7.

107. O'Rourke MGE, Wynne JM, Morahan RJ, Green AJ, Walker RM, Wilson ME. Prophylactic antibiotics in appendicectomy: a prospective double blind randomised study. *Aust NZ J Surg* 1984; **54**. 535–41.

108. Greenall MJ, Bakran A, Pickford IR *et al* A double-blind trial of a single intravenous dose of metronidazole as prophylaxis against wound infection following appendicectomy. *Br J Surg* 1979; **66**: 428–9.

109. Ingham HR, Sisson PR, Tharagonnet D, Selkon JB, Codd AA Inhibition of phagocytosis *in vitro* by obligate anaerobes *Lancet* 1977; **ii**: 1252–4.

110. Foster PD, O'Toole RD. Primary appendectomy: the effect of prophylactic cephaloridine on postoperative wound infection. *JAMA* 1978; **239**· 1411–2.

111. Berne TV, Yellin AW, Appleman MD, Heseltine PNR Antibiotic management of surgically treated gangrenous or perforated appendicitis *Am J Surg* 1982; **144**: 8–12.

112 Garcia GJ, Rodriguez RJM, Lozano SF *et al* Peri-incisional and preoperative administration of cefmetazole for the prophylaxis of wound infection after appendicectomy *Int Surg* 1986, **71**. 14–17

113 Silverman SH, Ambrose NS, Youngs DJ, Shepherd AFI, Roberts AP, Keighley MRB. The effect of peritoneal lavage with tetracycline solution on post-operative infection. *Dis Colon Rectum* 1986; **29**· 165–9.

114. Benson EA, Brown GJA, Whittaker M Prevention of wound infection in acute appendicitis. *Lancet* 1973; **ii**: 322.

115. Stewart DJ, Matheson NA. Peritoneal lavage in appendicular peritonitis. *Br J Surg* 1978; **65** 54–6.

116 Ivarsson LE. Single dose antibiotic prophylaxis in appendectomy. *Acta Chir Scand* 1977, **143**. 469–72.

117 Lally KP, Trettin JC, Torma MJ. Adjunctive peritoneal lavage in experimental peritonitis. *Surg Gynecol Obstet* 1983; **156**. 605–8.

118. Jones PF. *Acute appendicitis. Emergency Abdominal Surgery*, 2nd ed. Oxford: Blackwell, 1987; 91.

Paper accepted 11 April 1988

Br. J. Surg. 1988, Vol. 75, October, 1034

Transverse submammary skin incision for thyroidectomy

M. A. C. Aghaji

Department of Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria
Correspondence to: Dr M. A. C Aghaji

The low collar incision is the usual route for thyroidectomies because it allows excellent access to the thyroid gland and heals well. However, many African patients develop keloid scars. Moreover, such an overtly visible 'cut throat' scar in a young woman constitutes a taboo in many areas. Bilateral submammary skin incision with development of a flap that includes the subcutaneous tissue and the breasts allows good exposure of the thyroid for thyroidectomy.

Our experience with this unique approach is presented.

Patients and methods

Between January 1985 and December 1987, 32 women between the ages of 19 and 35 years with simple goitre, had thyroidectomy through the submammary approach.

The approach is started as described by William and Hanlon for median sternotomy using a transverse submammary skin incision[1]; it was popularized by Bedard *et al.*[2] and Laks and Hammond[3]. Once the suprasternal space of Burns is reached, two Dever retractors are applied under the flap to aid in the dissection of the flap over the thyroid gland. Using both blunt and sharp dissection, the flap over the strap muscles is split in the median plane to expose the pretracheal fascia. Thyroidectomy is carried out in the usual fashion and haemostasis is secured. A long tube drain is inserted and passed out through the stab wound below the lower skin incision The strap muscles are closed loosely above and left open below so that the thyroid cavity communicates freely with the space below the flap; two Redivac (O E C. Orthopaedic) drains are left under the flap. The flap is tagged onto the chest wall in three places on each side. Subcutaneous stitches must be placed in an interrupted fashion.

Results

There were no hospital or late deaths. The mean follow-up is 21·4 months. Thyroidectomy was successfully done in all patients. All patients left hospital 5–7 days after operation. There was no major wound infection or necrosis of the flap.

In 15 patients (47 per cent) hypertrophic scars started to develop; these were reduced by timely intralesional injection with triamcinolone. Two patients (6 per cent) had loss of cutaneous sensation around the lateral aspect of the skin incision.

Discussion

The low collar incision is the standard approach to the thyroid gland. It gives the quickest and most complete exposure for all thyroid and parathyroid operations. Unfortunately, in the African, ugly hypertrophic and keloid scars which are detrimental to the quality of life may develop after a low collar incision. This can be avoided by approaching the thyroid gland through a bilateral submammary incision which is feasible and without any added significant morbidity or mortality, while the scar, whether ugly or hypertrophic, is hidden under the breasts. The submammary approach has been used extensively in female patients undergoing sternotomy for cardiac operations with excellent results.

This approach to the thyroid gland is recommended for the consenting cosmetically conscious female patient under 35 years who is likely to develop visible ugly or hypertrophic scars after a low collar incision. Breast function is unlikely to be affected. The loss of cutaneous sensation near the incision experienced by two patients in the series resolved with time and did not constitute any discomfort to the patients.

In conclusion, the bilateral submammary skin incision as a route to thyroidectomy gives excellent results, provided that meticulous attention is paid to haemostasis in the flap, extensive lateral mobilization, adequate drainage and careful closure with a subcuticular suture.

References

1. William WL, Hanlon CR. Median sternotomy using a transverse submammary skin incision. *Am J Surg* 1960; **100**: 79.
2. Bedard F, Keon WJ, Brais MP, Goldstein W. Submammary skin incision as a cosmetic approach to medical sternotomy *Ann Thorac Surg* 1986, **41**· 339–41.
3. Laks H, Hammond GL. A cosmetically acceptable incision for the median sternotomy *J Thorac Cardiovasc Surg* 1980; **79**: 146–9.

Paper accepted 22 May 1988

Br. J. Surg. 1988, Vol. 75, October, 1035

Macro-amylasaemia as a cause of persistently raised serum amylase

P. A. Andrews and P. A. Thomas

Department of Surgery, Whipps Cross Hospital,
Leytonstone, London E11 1NR, UK
Correspondence to: Mr P. A. Thomas

Not all patients with abdominal pain, raised serum amylase and proven gallstones have acute pancreatitis secondary to biliary tract disease. We describe such a case.

Case report

A 43-year-old woman presented with a short history of epigastric pain. Examination revealed a fit-looking woman with a normal abdomen. Full blood count, urea and electrolytes, erythrocyte sedimentation rate, glucose, urinalysis, abdominal radiograph and chest radiograph were all normal. Liver function tests were normal except for a slightly raised total bilirubin of 35 μmol/l (normal range 3–18 μmol/l). Serum amylase was 1160 units/l (normal 450 units/l). An abdominal ultrasound showed a distended gallbladder with stones in the neck but no dilatation of the common bile duct and no pancreatic abnormality. A diagnosis of acute pancreatitis secondary to gallstones was made and she responded rapidly to intravenous fluids and pain relief with return of liver function to normal within 3 days. However, sequential serum amylase levels remained persistently high (range 650–1760 units/l).

A repeat ultrasound and computer tomography (CT) scan showed no evidence of pancreatic inflammation or biliary obstruction. After discharge she was re-admitted to hospital twice in the next 2 months. The clinical picture was similar on each occasion. Initial serum amylase levels were 1600 and 840 units/l on respective presentations, and varied during this time from 840 to 1600 units/l.

Recurrent attacks of acute pancreatitis were diagnosed by separate on-call surgical registrars and she was admitted for conservative management on each occasion. An abdominal CT and endoscopic retrograde cholangiopancreatography showed no significant abnormality except for gallbladder stones.

When it became apparent that her serum amylase was not going to settle, an elective cholecystectomy was performed. She was found to have sub-acute cholecystitis with pigment stones and a normal peroperative cholangiogram. A laparotomy was otherwise normal. Her postoperative recovery was unremarkable, but the serum amylase levels remained high.

It now became clear that her hyperamylasaemia was unlikely to be secondary to biliary tract disease and it was surmised that her raised serum amylase and gallstones might be coincidental findings. A review was undertaken of known causes of hyperamylasaemia and, by exclusion, macro-amylasaemia became a distinct possibility in this patient.

The diagnosis of macro-amylasaemia was established in three stages. Firstly, as macromolecules are not filtered at the glomerulus, the high serum amylase in macro-amylasaemia is not reflected by a similarly raised urine amylase activity. In the presence of normal renal function, the clearance ratio of amylase may be calculated in the following way:

$$\text{Clearance ratio } (\%) = \frac{\text{urine amylase activity} \times \text{serum creatinine concentration}}{\text{serum amylase activity} \times \text{urine creatinine concentration}} \times 100$$

The normal range is 1–4 per cent and may rise to 4–15 per cent in acute pancreatitis; in macro-amylasaemia the figure is <1 per cent[1]. Our patient had a clearance ratio of 0·4 per cent.

Secondly, a rapid and simple assay for the presence of macro-amylase involves the selective precipitation of macromolecules in polyethylene glycol solution[2]. In a normal subject 33 per cent of amylase activity is precipitated, whereas in macro-amylasaemia the figure is 73 per cent. Our patient registered 98 per cent.

Finally, definitive diagnosis involves the direct identification of the amylase-macromolecular complex by one of several physical methods. This was performed using a method of agarose film electrophoresis[3] and gave the typical streaked appearance of macro-amylasaemia. It was concluded from this information that a firm diagnosis of macro-amylasaemia had been established.

Discussion

Macro-amylasaemia is a benign condition of persistently raised serum amylase activity with no apparent clinical symptoms of pancreatic disorder[4]. It occurs when 'free' circulating amylase forms a complex with a naturally occurring macromolecule, usually IgG or IgA (or occasionally infused dextran), which is too large to be normally filtered in the renal glomerulus. A hyperamylasaemia therefore occurs typically in the range 1–5 times normal. The condition occurs in approximately 1 per cent of the normal population and in up to 10 per cent of cases of persistently raised serum amylase[3]. Macro-amylasaemia should be suspected in any patient with hyperamylasaemia and an atypical clinical presentation although macro-amylasaemia in itself is asymptomatic. The presence of gallstones in this patient must be taken as coincidental and in no way responsible for the abnormal amylase level. The diagnosis was initially supported by a very low (<1 per cent) amylase/creatinine renal clearance ratio in the presence of normal renal function. If serum lipase levels are available, the association of a normal lipase level with a raised serum amylase can also be strongly suggestive and would warrant further investigation. The presence of a macromolecule may be rapidly and simply confirmed by polyethylene glycol precipitation. Specific identification of the macromolecule as a conglomerate of amylase then follows by an electrophoretic technique. As the amylase macromolecules found in this condition may be formed from any of the pancreatic or salivary isoenzymes of amylase, isoenzyme analysis is of no help.

Acknowledgements

We should like to thank Dr P. Foley and Dr S. Rosalki (consultant chemical pathologists) for their assistance in the investigation of this patient.

References

1. Hendry JB. *Clinical Diagnosis and Management by Laboratory Methods*, 17th edn, London: W. B. Saunders, 1984: 538–41.
2. Levitt MD, Ellis C. A rapid and simple assay to determine if macroamylase is the cause of hyperamylasaemia. *Gastroenterology* 1982; **83**: 378–82.
3. Forsman RW. Macroamylase: prevalence, distribution of age, sex, amylase activity and electrophoretic mobility. *Clin Biochem* 1986; **19**: 250–3.
4. Fridhandler L, Berk JE. Macroamylasaemia. *Adv Clin Chem* 1978; **20**: 267–86.

Paper accepted 17 February 1988

0007–1323/88/101035–01$3.00

Br. J. Surg. 1988, Vol. 75, October, 1036

Persisting superior mesenteric artery syndrome following ileo-anal J pouch construction

P. M. Christie, D. Schroeder and G. L. Hill

Department of Surgery, Auckland Hospital, Park Rd, Auckland 1, New Zealand
Correspondence to: Professor G. L. Hill

Total colectomy and mucosal proctectomy, with formation of an ileo-anal reservoir, has become the preferred operation for treatment of chronic ulcerative colitis and familial polyposis in selected young patients. Prolonged ileus or small bowel obstruction is a common complication in the early postoperative period[1]. Recently, a new complication simulating small bowel obstruction of adhesive origin has been described: a case of postoperative superior mesenteric artery syndrome (SMAS)[2] which settled with conservative management. We present a further case of SMAS following restorative proctocolectomy which only resolved after further operation.

Case report

The patient was a 21-year-old man with severe refractory ulcerative colitis, who had lost 24 per cent of his body weight over the 6 months before admission. After failing to settle on a 10-day course of preoperative intravenous nutrition, semi-urgent laparotomy was performed.

Marked inflammation of the distal colon was noted. Total colectomy and mucosal proctectomy were performed, and an ileal J pouch constructed using the GIA® stapler. Transverse incisions were made in the peritoneum of the mesentery over the superior mesenteric artery, allowing the ileo-anal anastomosis to sit in the pelvis without tension. The defunctioning loop ileostomy similarly reached the right iliac fossa comfortably.

Initially his postoperative course was uneventful but, at 6 days, after the nasogastric tube had been removed and oral intake commenced, vomiting occurred and the nasogastric tube had to be replaced. Thereafter he continued to have copious bile-stained nasogastric aspirates, necessitating the re-introduction of intravenous nutrition at 10 days. A barium study showed a dilated duodenum with a band obstruction in the fourth part, consistent with SMAS (*Figure 1*). Intravenous nutrition was continued and various postures encouraged, but there was no decrease in the volume of the gastric aspirates (1·5–3·0 l/day). After allowing 6 weeks for intra-abdominal inflammation to settle, a further laparotomy was performed.

The duodenojejunal flexure was particularly high, held cephalad by a strong suspensory ligament of Treitz; the superior mesenteric artery was bowstringed across the duodenum just proximal to this. The ligament of Treitz was divided and the duodenojejunal flexure completely mobilized, then transposed to a position anterior to the superior mesenteric artery by dividing and re-anastomosing the bowel. The loop ileostomy was closed at the same operation.

The patient returned to a normal diet within 7 days, and was discharged 15 days after his second operation, in good control of his new pouch.

Discussion

Obstruction of the third part of the duodenum by the superior mesenteric artery is relatively uncommon, usually occurring in thin elderly people or in those who have recently lost retroperitoneal fat owing to stress of sepsis or trauma[3]. Many patients with ulcerative colitis have had a long illness and, at the time of presentation for surgery, have often suffered a significant loss of fat and protein, possibly setting up the physical state that allows the SMAS to occur[4]. This tendency to obstruction would be exacerbated by any extra tension on the artery created during ileo-anal anastomosis.

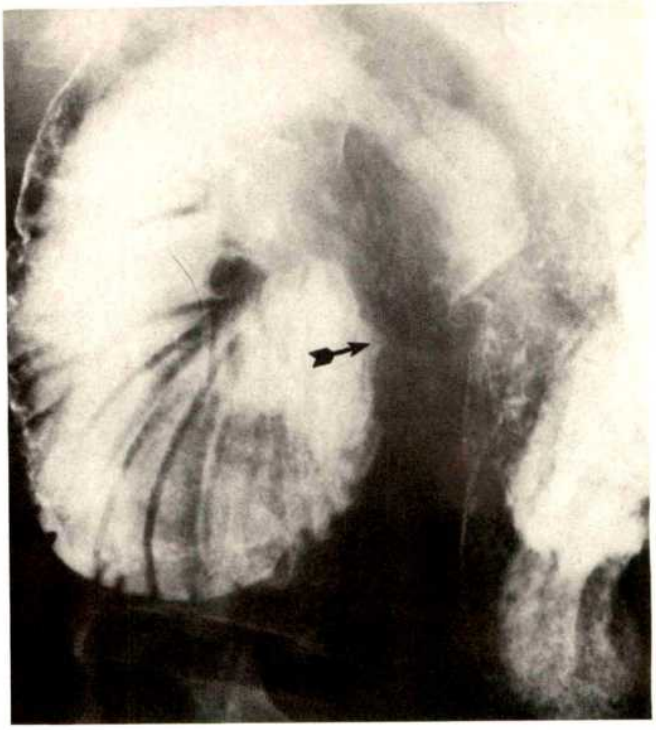


Figure 1 *Barium study performed 10 days postoperatively. There is complete obstruction of the duodenum at the point where it is traversed by the superior mesenteric artery (arrowed)*

There have been several suggestions as to how to lengthen a 'tight' artery. Most commonly the surgeon makes serial transverse cuts in the peritoneum overlying the artery on both sides, as was done in the case above. This increases the reach of the artery by up to 2 cm. The surgeon may also clamp the superior mesenteric artery distal to the jejunal branches; provided that the terminal ileum remains well perfused via the ileocolic artery, he may then divide it at this point. It is interesting to note that in both the previously reported case and our own patient, the surgeon was confident that the anastomosis was not under tension and there was no obstruction to the gut, before closing the abdomen. There is obviously difficulty in predicting which patients are at risk of developing SMAS so that further efforts can be made to prevent the problem. It is now our practice, like others[1], in addition to lengthening the ileal loop by division of the superior mesenteric artery and peritoneal incisions, to routinely mobilize both the duodenal loop and the duodenojejunal flexure thoroughly.

References

1. Taylor BA, Dozois RR. The J ileal pouch–anal anastomosis. *World J Surg* 1987; **11**: 727–34.
2. Ballantyne GH, Graham SM, Hammers L, Modlin IM. Superior mesenteric artery syndrome following ileal J-pouch anal anastomosis: an iatrogenic cause of early postoperative obstruction. *Dis Colon Rectum* 1987; **30**: 472–4.
3. Wayne E, Miller RE, Eisman B. Duodenal obstruction by the superior mesenteric artery in bedridden combat casualties. *Ann Surg* 1971; **174**: 339–45.
4. Muller R. Quoted by Barner HB, Sherman CD Jr. Vascular compression of the duodenum. *Int Abstr Surg* 1963; **117**: 103–18.

Paper accepted 20 March 1988

GIA® is a registered trademark of Auto Suture Company.

0007–1323/88/101036–01$3.00

Br. J. Surg. 1988, Vol. 75, October, 1037–1038

Local antiseptic treatment of infected prosthetic vascular grafts in the groin

K. T. Moran and E. R. Jewell

Section of Peripheral Vascular Surgery, Lahey Clinic Medical Center, Burlington, Massachusetts, USA

Correspondence to: Dr E. R. Jewell, Section of Peripheral Vascular Surgery, Lahey Clinic Medical Center, 41 Mall Road, Burlington, Massachusetts 01805, USA

Prosthetic grafts have been in general use for aortobifemoral bypass for nearly 30 years, and when no suitable autogenous vein graft is available for femoropopliteal bypass. In either case, infection of an arterial prosthetic graft has been reported in from 1·1 per cent to 6 per cent of patients with about 80 per cent of these infections occurring in the groin[1–3].

The traditional therapeutic approach to this problem has been removal and replacement of the graft through clean tissue planes. However, infected grafts in the groin have been treated by local débridement and irrigation of the wound combined with systemic antibiotic therapy[4] or by reconstruction within the infected field, replacing the infected graft with arterial or venous autografts[5].

Polyvinylpyrrolidone complexed with iodine (povidone–iodine or Betadine*) does not adversely affect healing tissues[6] and laboratory studies indicate that it does not induce the production of antibiotic-resistant strains of organisms[7].

In 1981 Kwaan and Connolly[8] successfully treated ten consecutive patients with open infections of vascular prosthetic graft wounds with a povidone–iodine irrigation method supplemented by intravenous antibiotics. We report similar treatment in two patients with infected inguinal prosthetic grafts.

Case reports

Case 1

A 71-year-old man underwent endarteriectomy of the left common femoral and profunda femoris arteries and *in situ* femoroperoneal saphenous vein bypass graft for ischaemic ulceration involving the left great toe. A polytetrafluoroethylene (PTFE) patch angioplasty was used to close the arteriotomy, which extended from the external iliac artery to the profunda femoris artery. Postoperatively, the ulcer began to heal, and the patient was discharged from the hospital after 7 days. Two weeks later, the patient presented with swelling, erythema, and fluctuance in the groin incision. After incision and drainage, the wound was completely débrided, exposing the PTFE patch angioplasty and the proximal end of the vein graft, which was patent (*Figure 1*). Systemic antibiotic therapy with cephalothin sodium and gentamicin sulphate was commenced, and the wound was packed with gauze soaked in half-strength povidone–iodine solution. *Proteus mirabilis*, cultured from the wound, showed sensitivity to the antibiotics employed. Dressings were changed daily. The patient was observed in the intensive care unit until the eighth postoperative day when granulation tissue covered all vascular conduits. Two weeks later, the patient was discharged with a healthy granulating wound (*Figure 2*). At follow-up 8 weeks after the operation, the wound had completely healed. Two years later, the patient remains well, and the graft is patent.

Case 2

Aortobifemoral bypass using a Dacron® graft was performed on a 72-year-old man for an abdominal aortic aneurysm and occlusive iliac disease. On the third postoperative day, he experienced a myocardial infarction and became hypotensive. Despite maximum doses of pressor agents, he remained hypotensive and required an intra-aortic balloon pump which was inserted through the Dacron graft in the left groin and left *in situ* for 2 days. He made satisfactory progress but on the 12th postoperative day was noted to have an abscess in the left groin. The patient was treated with oxacillin, gentamicin sulphate, and metronidazole. The wound was débrided, exposing the prosthetic graft. Organisms cultured from the wound included *Morganella morganii*, *Enterobacter cloacae*, and enterococcus, which were sensitive to the antibiotics used. The wound was packed with gauze and soaked in half-strength povidone–iodine, and the dressings were changed daily. The patient was observed in the intensive care unit until the graft was completely covered by granulation tissue 10 days later. He remained in the hospital for an additional week. At follow-up 1 year later, the graft was patent and the wound completely healed.

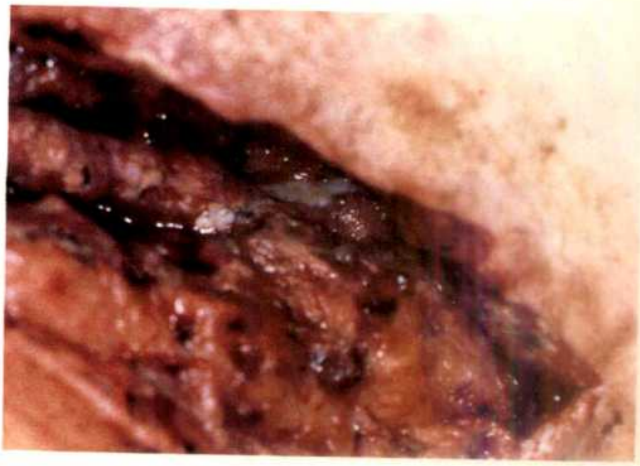


Figure 1 *Infected wound with polytetrafluoroethylene patch and vein graft exposed*

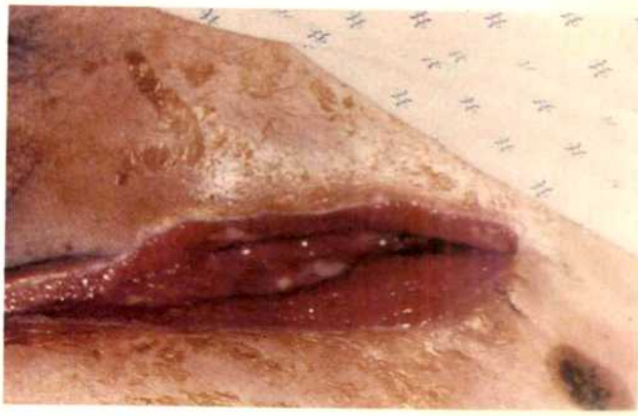


Figure 2 *Wound healing by secondary intention after 10 days of povidone–iodine treatment*

Discussion

Infection of a prosthetic graft is usually an extremely grave problem involving the threat of generalized sepsis, haemorrhage, and limb loss, with a mortality rate varying from 25 to 75 per cent in reported series[3,9]. Carter *et al.*[10] first demonstrated that exceptions exist to the widely respected rule that the successful management of an infected graft demands its removal. The successful treatment of a patient with an infected graft depends on many variables including the site and extent of infection, the location of the graft, anastomotic involvement, and graft patency[11]. Our finding that infected grafts in the groin may be preserved if the graft is patent is similar to that of other authors[5,8]. The type of prosthetic graft used may influence the outcome. Bacteria have been shown to have a greater affinity for adhering to knitted and woven Dacron grafts than to polytetrafluoroethylene[12]. Open management of the wound and healing by secondary intention permit the constant observation and meticulous nursing care necessary to detect haemorrhage from the suture line, which is an absolute indication for removal of the graft. The success of open management in this context contrasts with the poor long-term results obtained when this method is used after traumatic vascular injuries probably because of the extensive soft tissue injuries sustained in the latter group[13]. Previous reports[6–8] indicate that the antiseptic action

---

** Betadine is manufactured by Napp Laboratories Ltd., Cambridge, UK; Dacron® is a registered trademark of E. I. Dupont de Nemour Incorporated*

0007-1323/88/101037-02$3.00

of povidone–iodine is rapidly diminished on contact with tissue or serum. Nevertheless, in our patients, a single daily change of the pack resulted in rapid cleansing and granulation of open wounds. In selected patients, local treatment may eliminate the need for major surgical procedures in seriously ill patients.

References

1. Goldstone J, Moore WS. Infection in vascular prostheses: clinical manifestations and surgical management. *Am J Surg* 1974; **128**: 225–33.
2. Jamieson GG, DeWeese JA, Rob CG. Infected arterial grafts. *Ann Surg* 1975; **181**: 850–2.
3. Szilagyi DE, Smith RF, Elliott JP, Vrandecic MP. Infection in arterial reconstruction with synthetic grafts. *Ann Surg* 1972; **176**: 321–33.
4. Popovsky J, Singer S. Infected prosthetic grafts: local therapy with graft preservation. *Arch Surg* 1980; **115**: 203–5.
5. Ehrenfeld W, Wilbur B, Olcott CN, Stoney J. Autogenous tissue reconstruction in the management of infected prosthetic grafts. *Surgery* 1979; **85**: 82–92.
6. Connell JF Jr, Rousselot LM. Povidone–iodine. Extensive surgical evaluation of a new antiseptic agent. *Am J Surg* 1964; **108**: 849–55.
7. Gilmore OJ, Sanderson PJ. Prophylactic interparietal povidone–iodine in abdominal surgery. *Br J Surg* 1975; **62**: 792–99.
8. Kwaan JH, Connolly JE. Successful management of prosthetic graft infection with continuous povidone–iodine irrigation. *Arch Surg* 1981; **116**: 716–20.
9. Hoffert PW, Gensler S, Haimovici H. Infection complicating arterial grafts: personal experiences with 12 cases and review of the literature. *Arch Surg* 1965; **90**: 427–35.
10. Carter SC, Cohen A, Whelan TJ. Clinical experience with management of the infected Dacron graft. *Ann Surg* 1963; **158**: 249–55.
11. Liekweg WG Jr, Greenfield LJ. Vascular prosthetic infections: collected experience and results of treatment. *Surgery* 1977; **81**: 335–42.
12. Schmitt D, Bandyk D, Pequet A, Towne J. Bacterial adherence to vascular prostheses. *J Vasc Surg* 1986; **3**: 722–40.
13. Feliciano DV, Mattox KL, Graham JM, Bitondo CG. Five-year experience with PTFE grafts in vascular wounds. *J Trauma* 1985; **25**: 71–82.

Paper accepted 12 February 1988

Br. J. Surg. 1988, Vol. 75, October, 1038–1039

Rare congenital anomaly of the portal vein

A. D. Joyce and E. R. Howard

King's College Hospital, London SE5 9RS, UK

Correspondence to: Mr E. R. Howard, Firm III Office,
King's College Hospital, Denmark Hill, London
SE5 9RS, UK

Anomalous venous connections between the portal vein and the inferior vena cava have been described[1], but have received little clinical attention. Their overall frequency is unknown but anomalies are probably less uncommon than the literature would suggest. Recently we encountered a rare variation whereby the portal vein drained into the inferior vena cava (congenital portacaval shunt) in a 10-year-old girl who underwent an 85 per cent trisegmentectomy of the liver for hepatocellular carcinoma. This paper discusses the development and clinical implications[2] of congenital anomalies of the portal venous system.

Case report

A 10-year-old girl born with co-arctation of the aorta and patent ductus arteriosus, which was surgically corrected at the age of 3 years, presented with periumbilical pain and diarrhoea of 3 months duration.

Height and weight were below the third centile. In the abdomen, the right lobe of the liver was palpable 7 cm below the costal margin. Peripheral blood count, serum biochemistry and α-fetoprotein estimations were normal. Liver function tests showed alkaline phosphatase 303 units/l, AST* 182 units/l, gGT* 132 units/l, bilirubin 34 μmol/l. Ultrasound and isotope studies revealed a lesion occupying the right lobe of the liver compressing the inferior vena cava. This was confirmed on selective angiography demonstrating a large vascular hepatic tumour. There was no evidence of metastatic spread. Laparotomy confirmed an extensive vascular tumour involving the whole of the right lobe including the caudate and quadrate regions. The spleen was noted to be twice normal size and the portal vein emptied directly into the inferior vena cava just proximal to the origin of the renal veins. An 85 per cent trisegmentectomy was performed with complete excision of the mass.

The patient made a satisfactory recovery and the histology of the tumour demonstrated well-differentiated hepatocytes consistent with a well-differentiated hepatocellular carcinoma. Subsequent splenic venography has documented the anomaly of the portal venous system (*Figure 1*). Serum ammonia estimation and a psychiatric assessment were performed to exclude subclinical encephalopathy. These were normal and at 4 years follow-up she remains free of any local recurrence or metastatic disease.

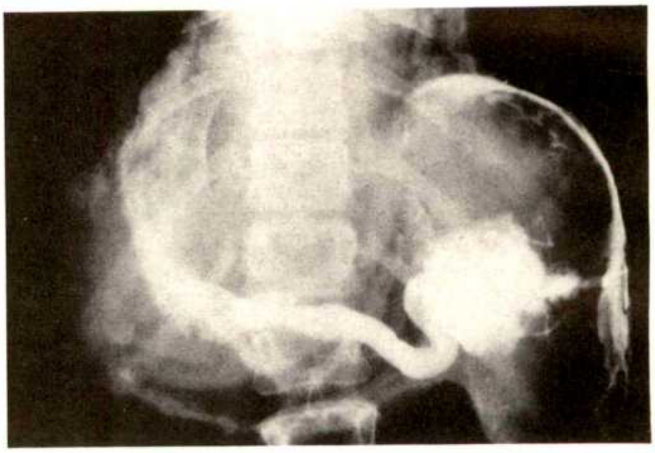


Figure 1 *Splenic venogram demonstrating that the splenic vein drains directly into the inferior vena cava. (The inferior vena cava is displaced to the right)*

Discussion

This case illustrates a rare anatomical variant of the portal venous system with important implications for hepatic regeneration after surgery and the risk of the late onset of encephalopathy.

The venous system of the body arises from essentially two main sources. The first is intra-embryonic, comprising the anterior and posterior cardinal veins from which the main systemic veins subsequently develop. The second source is extra-embryonic, the vitelline and umbilical venous system, providing drainage from the yolk sac and placenta respectively[3,4].

The vitelline veins develop to form the portal vein. These primitive paired vessels arise on the anterior surface of the yolk sac and pass up the body to empty into the primitive sinus venosus. By the end of the fourth week *in utero*, three cross-communications have formed between the two veins (*Figure 2*). The cranial anastomosis lies in the region of the porta hepatis (subhepatic plexus), the middle passes dorsal to the gut (i.e. retroduodenal) while the inferior communication arises distal to the origin of the common bile duct and passes ventrally. The portal vein derives from the inferior section of the left vitelline vein, the middle communication and the superior section of the

---

**AST, aspartase transaminase; gGT, γ-glutamyl transpeptidase; CSF, cerebrospinal fluid*

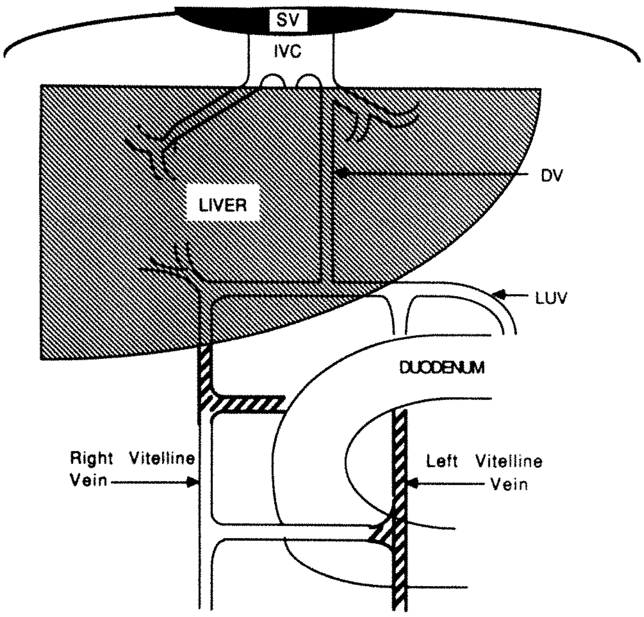


Figure 2 *Embryological development of the portal vein and relationship to the duodenum. DV, ductus venosus; IVC, inferior vena cava; LUV, left umbilical vein; SV, sinus venosus*

right vein, thus forming an 'S' shape configuration[1,4]. The remaining pathways atrophy.

Abnormalities of the portal venous system arise from alterations in the configuration forming the portal vein and are a secondary association with a variety of other congenital malformations (*Table 1*)[5]. Other anomalies can arise from normally insignificant but potentially lethal collateral communications between the extrahepatic and intrahepatic branches of the portal and systemic venous system[6]. Classically these include the gastro-oesophageal anastomosis, and the anorectal, periumbilical and retroperitoneal communications. Abnormalites of the portal vein include the preduodenal portal vein and reduplication. Rarely the portal vein enters directly into the inferior vena cava without traversing the liver.

The origin of the inferior vena cava is complex and is an amalgamation of several embryological venous channels. The common hepatic vein which gives rise to the hepatic segment of the inferior vena cava arises from the right end of the sinus venosus and the right portion of the plexus which joins the right and left vitelline veins in the cranial part of the liver (subdiaphragmatic anastomosis)[4]. During fetal development blood from the left umbilical vein reaches this anastomosis and the common hepatic vein via the ductus venosus. The subhepatic portion of the inferior vena cava is formed from outgrowths of both the common hepatic vein and the right subcardinal vein.

The complicated origin of the prerenal section of the inferior vena cava and its close developmental relationship to the plexiform subdiaphragmatic anastomosis of the vitelline veins in the early embryo helps to explain the occasional occurrence of anomalous portosystemic venous communications. A review of the literature reveals four previous cases which were discovered at autopsy[7-10]. Our case is the first to be described in a living patient.

Portal encephalopathy has been seen occasionally in patients without liver disease who have a prominent intra- or extrahepatic fistulous communication with a systemic vein, usually in association with portal hypertension[11]. This condition is analogous to the neuropsychiatric disturbance seen in patients with an Eck's fistula[12]. The clinical syndrome presents as an episodic encephalopathy involving ataxia, tremor and dysarthria and the patients are usually over 50 years of age with normal serum ammonia levels but elevated CSF* glutamine. If recognized, the condition is potentially curable because the cerebral pathological changes are slight, but in a few patients the disorder is progressive and irreversible[13]. Why these symptoms become manifest late in life is unknown but it has been suggested that the ageing brain has a reduced tolerance to ammonia and other metabolites.

Table 1 *Malformations associated with portal vein anomalies*

Gastrointestinal tract	Malrotation Duodenal atresia Biliary atresia Annular pancreas
Cardiovascular	Situs inversus Cardiac anomalies

In 1920 Rous and Larimore suggested that substances in the portal venous blood prevented atrophy and promoted liver regeneration, while Child *et al.* (1953) believed that the volume of portal blood flow to the liver was important[14,15].

Experimental work has shown that hepatic tissue perfused with the venous return from the splanchnic organs undergoes hypertrophy, hyperplasia and glycogenation, whereas hepatocytes in tissue deprived of this input become smaller and have a reduced glycogen content[16]. Thus, in animals, it appears that portal venous blood has special properties that affect both hepatocellular structure and function[17]. Studies have shown that insulin, glucagon and epidermal growth factor appear to be the most important in the regulation of hepatic regeneration[18]. It is assumed that hepatic regeneration in this case has been stimulated by circulating hepatotrophic factors and the successful outcome suggests that liver resection is not contraindicated in patients with large congenital portosystemic communications.

References

1. Mark C. Developmental basis of the portal venous system. *Am J Surg* 1969; **117**: 671–81.
2. Starzl TE, Porter KA, Kashiwagi N *et al.* Portal hepatotrophic factors. Diabetes mellitus and acute liver atrophy, hypertrophy and regeneration. *Surg Gynecol Obstet* 1975; **141**: 843–58.
3. Gray SW, Skandalakis JE. *Embryology for Surgeons.* Philadelphia: WB Saunders, 1972: 177.
4. Dickson AD. The development of the ductus venosus in man and the goat. *J Anat* 1957; **91**: 358–68.
5. Boles ET, Smith B. Preduodenal portal vein. *Pediatrics* 1961; **28**: 805–9.
6. Reichardt W, Butzow GH, Erbe W. Anomalous venous connections involving the portal system. *Cardiovasc Radiol* 1979; **2**: 41–6.
7. Abernethy J. Account of two instances of uncommon formation in the viscera of the human body. *Phil Trans* 1793; **B83**: 59–66.
8. Kirnan F. The anatomy and physiology of the liver. *Phil Trans* 1833; **B113**: 711–70.
9. Hellweg G. Congenital absence of intrahepatic portal venous system simulating Eck fistula. Report of a case with necropsy findings. *AMA Arch Path* 1954; **57**: 425–30.
10. Olling S, Olsson R. Congenital absence of portal venous system in a 50-year-old woman. *Acta Med Scand* 1974; **196**: 34–35.
11. Sherlock S. *Diseases of Liver and Biliary System*, 7th ed. Oxford: Blackwell Scientific Publications, 1985: 95.
12. McDermott WV Jr, Adams RJ. Episodic stupors associated with an Eck fistula in the human with particular reference to the metabolism of ammonia. *J Clin Invest* 1954; **33**: 1–9.
13. Raskin NH, Bredesen J, Ehrenfeld WK *et al.* Periodic confusion caused by congenital extrahepatic portocaval shunt. *Neurology* 1984; **34**: 666–9.
14. Rous P, Larimore LJ. Relation of the portal blood to liver maintenance: a demonstration of liver atrophy conditional on compensation. *Proc Soc Exp Biol Med* 1919–1920; **17**: 65.
15. Child CS, Barr T, Holowade GR *et al.* Liver regeneration following portocaval transposition in dogs. *Ann Surg* 1953; **138**: 600–8.
16. Starzl TE, Francavilla A, Halgrimson CG *et al.* Origin, hormonal nature and action of hepatotrophic substances in portal venous blood. *Surg Gynecol Obstet* 1973; **137**: 179–98.
17. Rozga J, Jepsson B, Bengmark S. Hepatotrophic factors in liver growth and atrophy. *Br J Exp Path* 1985; **66**: 669–78.
18. Baker AL. Hepatotrophic factors: Basic concepts and clinical implications. *Acta Med Scand* 1985; **703** (Suppl.): 201–8.

Paper accepted 5 May 1988

Br. J. Surg. 1988, Vol. 75, October, 1040–1041

Bacteriology of mammary duct ectasia

R. J. Aitken, J. Hood*, J. J. Going†, R. S. Miles* and A. P. M. Forrest

*The University Department of Surgery,
The Royal Infirmary, Edinburgh and The University
Departments of *Bacteriology and †Pathology,
Medical School, Edinburgh, UK*

Correspondence to: Professor Sir Patrick Forrest,
University Department of Surgery, The Royal Infirmary,
Edinburgh EH3 9YW, UK

The role of infecting organisms in initiating or complicating mammary duct ectasia and its related change of periductal mastitis remains uncertain. Some believe that mammary duct ectasia is a natural phenomenon of the ageing breast[1] and this is supported by reports of occult duct ectasia in 25–75 per cent of breasts examined at post mortem in women in whom there has been no previous breast disorder[2-3]. Others suggest that ductal dilatation occurs as a consequence of episodes of infection within the breast leading to destruction of elastica in the duct wall[4]. Evidence for this view is the recent finding that, contrary to previous reports[5,6], organisms, particularly anaerobes, can be identified in the nipple discharges as well as purulent exudates (e.g. from mammillary fistulae) which can be associated with this condition.

The aim of the present study was to ascertain whether there was any evidence of similar infecting organisms in women with proven histological mammary duct ectasia without clinical evidence of inflammatory complications who did not have a history of previous breast infection.

Patients and methods

Twenty-five women without previous breast disease undergoing surgery for a variety of breast conditions in whom at operation it was feasible to remove a sample of breast tissue from behind the nipple areolar complex were studied. All operations were carried out by the same surgeon (R.J.A.) who recorded whether there was gross evidence of duct ectasia (dilated ducts) containing inspissated secretions (Group 1). Group 2 had no such macroscopic evidence of duct ectasia. A swab of that area was taken and placed in Robertson's cooked meat broth[7-9]. A sample of breast tissue and the swab were immediately transported to the Department of Bacteriology for culture and for identification of organisms detected by the methods previously described[9]. The remaining tissue was sent for pathological examination.

Results

Eleven of the 25 women had duct ectasia recognized at operation and confirmed histologically (Group 1). The remaining 14 (Group 2) had no such macroscopic evidence of duct ectasia and this was confirmed histologically in 12; the remaining two patients in Group 2 had mild duct dilatation but no associated inflammation. The clinical presentation and pathological diagnosis of the patients leading to the finding of occult duct ectasia is given in *Table 1*.

Table 1 *Clinical and pathological details*

	Group 1	Group 2
Age: median (years)	44·4	38·3
range (years)	28–62	27–76
Clinical presentation		
Discrete mass	7	7
Breast thickening	4	4
Blood nipple discharge	0	2
Recurrent cyst	0	1
Pathological diagnosis		
Normal breast	0	2
Dysplastic breast	1	1
Fibro-adenoma	1	5
Phylloides tumour	1	0
Carcinoma	6	2
Duct papilloma	0	2
Other	2	2

Bacteriological findings are given in *Table 2* both for culture of tissues and swabs. Neither anaerobic bacteria nor enterococci were identified from any patient. *Staphylococcus aureus* was reported in three patients (2 tissues, 2 swabs) and a coagulase-negative *Staphylococcus* reported in 13 (6 tissues, 13 swabs).

Details of the histological findings are also given in *Table 2* but there was no relationship to the presence or absence of significant organisms. Active periductal mastitis was present in the absence of identifiable infecting organisms.

Discussion

This study has demonstrated that uncomplicated mammary duct ectasia found as an incidental phenomenon within the breast is sterile even when there is histological evidence of periductal mastitis. As none of these women had a previous history of breast inflammation it is unlikely that these changes are a response to previous infection. However, we have previously demonstrated that when patients with duct ectasia present with a clinically evident infection (e.g. a circumareolar abscess, mammary fistula) or with a nipple discharge, organisms, and particularly anaerobes, may be identified[7]. Whether these two studies represent patients with differing aspects of the same disease spectrum is unclear.

The finding of coagulase-negative staphylococci in 6 tissues and 13 swabs is considered to be of doubtful significance. These organisms are common skin commensals and their presence here is perhaps merely indicative of contamination of the swab or tissue during the sampling procedure.

This study supports the view that so-called occult duct ectasia, as has been described in normal breasts at post mortem, is not the result of an infective process but represents an involutionary change in the ageing breast. The lack of correlation between histological evidence of periductal mastitis and the bacteriological studies suggests that these changes are not of infective origin, at least not from common organisms. The relationship between duct ectasia, periductal mastitis and clinical infection of the major ducts leading to periareolar sepsis is still not clear.

References

1. Haagenson CD. *Diseases of the Breast*, 3rd edn. Philadelphia: Saunders, 1981: 357–68.
2. Frantz UK, Picken JW, Melcher GW *et al*. Incidence of chronic cystic disease in so-called 'normal' breasts: a study on 225 post mortem examinations. *Cancer* 1981; **4**: 762–83.
3. Thomas WG, Williamson RCN, Davies JD, Webb AJ. The clinical syndrome of mammary duct ectasia. *Br J Surg* 1982; **69**: 423–5.
4. Bonser GM, Dossett JA, Jull JW. *Human and Experimental Breast Cancer*. London: Pitman Medical, 1961: 237–65.

0007-1323/88/101040-02$3.00 © 1988 Butterworth & Co (Publishers) Ltd

Table 2 *Relationship of mammary duct ectasia to swab and tissue culture*

	Histology		Bacteriology		
Patient	Dilated ducts	Periductal mastitis	*Staphylococcus aureus*	Coagulase-negative Staphylococcis	Other
Group 1					
1	+	No			
2	++	Severe			
3	+++	No		T,S	
4	++	Mild			
5	+	No		S	
6	++	No		T,S	
7	++	No		T,S	
8	++	Mild		T,S	
9	++	Mild		T,S	Diphtheroids
10	++	Mild	T,S		
11	++	No			
Group 2					
1	–	No		S	
2	–	No	T	S	
3	–	No			Diphtheroids
4	–	No		T,S	
5	+	No		S	
6	–	No	S		
7	–	No			
8	–	No			
9	–	No			
10	–	No		S	
11	+	No			
12	–	No		S	
13	–	No			
14	–	No		S	

T, tissue culture; S, swab. Degree of duct dilatation; +, mild, ++, moderate; +++, severe

5. Walker JC, Sandison AT. Mammary duct ectasia. *Br J Surg* 1964; **51**: 350–5.
6. Ewing M. Stagnation in mammary ducts of the breast. *J R Coll Surg Edinb* 1963; **8**: 134–42.
7. Bundred NJ, Dixon JMJ, Lumsden AB *et al.* Are the lesions of duct ectasia sterile? *Br J Surg* 1985, **72**· 844–5.
8. Dixon JM, Anderson TJ, Lumsden AB, Elton RA, Roberts MM, Forrest APM. Mammary duct ectasia *Br J Surg* 1983, **70**. 601–3
9. Miles RS, Hood J, Bundred NJ *et al* The role of Robertson's cooked meat broth in the bacteriological evaluation of surgical specimens. *J Med Microbiol* 1985; **20**· 373–8.

Paper accepted 23 May 1988

Br. J. Surg. 1988, Vol. 75, October, 1041–1042

Recurrent laryngeal nerve palsy associated with thyroiditis

M. E. Lucarotti and R. T. J. Holl-Allen

Department of Surgery, East Birmingham Hospital, UK
Correspondence to: Miss M E. Lucarotti, University
Department of Surgery, Southmead Hospital,
Bristol BS10 5NB, UK

Vocal cord paralysis is associated with malignant thyroid disease with an incidence of 11·3 per cent[1]. It is rarely found in association with benign diseases of the thyroid. In the same series of 1200 thyroidectomies a figure of 0·69 per cent was recorded. The association of recurrent nerve palsy and thyroiditis is even rarer. Six cases of thyroiditis complicated by vocal cord paralysis are now reported.

Patients and methods

The six patients were seen during the period 1965–1985. There were four women and two men with an age range 27–68, mean 43 years (*Table 1*). All underwent exploration of the thyroid as malignancy was suspected on clinical and isotopic scan evidence Four of the patients presented with voice changes. Four patients had had symptoms for less than a month. Two patients had no voice change symptoms despite a paralysed cord, one with Riedel's and one with Hashimoto's thyroiditis. In four patients the gland was affected mainly on one side; in each case the cord was paralysed on the ipsilateral side. Four patients had positive antibody titres, three with Hashimoto's and one with de Quervain's thyroiditis. All six patients had raised erythrocyte sedimentation rates. One patient with Hashimoto's disease was biochemically hypothyroid; the remainder were euthyroid.

Discussion

Recurrent nerve paralysis in benign thyroid disease is very uncommon. In such cases it is usually associated with multinodular goitre[2] and in both this and thyroiditis either side may be affected[1]. The apparent involvement of the recurrent nerve in thyroiditis is rare. Various authors have doubted the existence of the association[3,4]. Others are of the opinion that recurrent laryngeal nerve palsy suggests malignancy[5,6]. The mechanism of recurrent nerve paralysis associated with benign thyroid diseases is obscure but numerous theories have been put forward including stretching over the thyroid swelling[7] and calcification or inflammation[1]. Others suggested that pressure of the nerve against the goitre or trachea could be responsible[8–10]. Inflammation and subsequent fibrosis may be the cause in

0007-1323/88/101041-02$3 00

Table 1 *Clinical details of patients presenting with thyroiditis and recurrent laryngeal nerve palsy*

Patient	Age	Sex	Indication for surgery	Radio-isotope scan	Gland	Cord	Voice	Erythrocyte sedimentation rate	Antibody	Histology
1	49	F	? Malignancy	Minimum uptake	Diffuse	R	Normal	14	Normal	Riedel's
2	31	F	? Malignancy	Cold nodule	Diffuse ≫R	R	Normal	28	(Postop) >1 2500 Tanned RBC ANF weak	Hashimoto's
3	68	F	? Malignancy (recurrent Hurthle)	No uptake	L side	L	Change	40	Normal	Riedel's
4	38	F	? Malignancy R	Cold nodule R	Diffuse ≫R	R	Change	28	(Postop) >1·12 500 Tanned RBC	de Quervain's
5	27	M	Malignancy	No uptake	Isthmus hard	R	Change	25	(Postop) >1·12 500 Tanned RBC	Hashimoto's
6	44	M	Malignancy could not be excluded	No uptake R side	Hard R lobe	R	Change	18	1:25 000	Hashimoto's

R, right; L, left; ➤, greatest on; >, greater than; postop, postoperatively; RBC, red blood cells; ANF, anti-nuclear factor

thyroiditis particularly during the acute phase. However, the nature of the disease process precludes exploration of the nerve to confirm or refute this hypothesis

De Quervain's thyroiditis and cord palsy have only been recorded twice in the literature[2,11]. Cooke[12] found no cases of recurrent nerve palsy in six patients with Riedel's thyroiditis and felt that the nerves were never involved in this condition. However, others have noted an association[1,13]. Volpe and Johnson[14] reviewed 56 cases of thyroiditis. Eight patients presented with the symptoms of hoarseness but the aetiology or significance of this symptom was not clarified by laryngeal assessment.

Spontaneous paralysis of a vocal cord is rarely observed since laryngoscopic examination often is not performed in these patients and unilateral paralysis is asymptomatic in 30–50 per cent of cases[15,16]. Often no cause for the paralysis of the cord is found. Cunning[15] was unable to find a cause in 31 per cent of patients in a series of 262. It may be that some cases may be undiagnosed thyroiditis or idiopathic and totally unrelated[17,18].

Thyroiditis is a relatively rare condition but these cases serve to illustrate that a paralysed cord does not necessarily signify malignancy.

References

1. Holl-Allen RTJ. Laryngeal nerve paralysis and benign thyroid disease *Arch Otolaryngol* 1967; **85**: 335–7.
2 Langevitz P, Cavili S. Persistent vocal cord paralysis in subacute thyroiditis. *Postgrad Med J* 1983, **59**· 726–7.
3. Nager FR. Discussion of Brown-Kelly's paper. *Br Med J* 1927, **2**: 683
4. Blackburn G. Hoarseness in thyroid disease. *West J Surg Obst Gynaecol* 1955, **66**: 319–21.
5. Clerf LH. Unilateral vocal cord paralysis. *JAMA* 1953; **151**: 900–3.
6. Hoffenberg R. Autoimmune thyroiditis. *Br J Clin Pract* 1969; **23**. 257–60
7. Judd AF, New GB, Mann FC. The effect of trauma upon the laryngeal nerves. *Ann Surg* 1918; **67**: 257–72.
8. Joll CA, *Diseases of the Thyroid Gland* (*with Special Reference to Thyrotoxicosis*). London: Heinemann, 1932· 227
9. Rueger RG. Benign disease of the thyroid gland and vocal cord paralysis *Laryngoscope* 1974; **84**: 897–907.
10 Collett FJ. Paralysis of the larynx. *Ann d'Oto-laryng* 1937, **5**: 163.
11 Kallmeyer JC, Hackmann R. Vocal cord paralysis associated with subacute thyroiditis. *S Afr Med J* 1985; **67**: 1064
12 Cooke RV. Thyroid disease and thyroidectomy. *Ann R Coll Surg Engl* 1966; **39**: 201–12.
13. Greene R. Riedel's disease. *Br J Clin Pract* 1969; **23**: 261–3
14. Volpe R, Johnson MW. Subacute thyroiditis commonly mistaken for pharyngitis. *Can Med Assoc J* 1957; **77**: 297–307.
15. Cunning DS. Unilateral cord paralysis. *Ann Otol* 1955, **64**. 487–93.
16. Work WP Paralysis and paresis of the vocal cords. *Arch Otolaryngol* 1941, **34**. 267–80.
17 Faaborg-Anderson K. Recurrent laryngeal paralysis of unknown aetiology. *Acta Otolaryngol* (suppl Stockh) 1954, **118**. 68–75.
18. Worgan D, Saunders S, Jones J. Recurrent laryngeal nerve paralysis and the non-malignant thyroid. *J Laryngol Otol* 1974; **88**· 375–8.

Paper accepted 12 May 1988

Br. J. Surg. 1988, Vol. 75, October, 1043

Solitary cysts of the parotid

J. D. Maynard

Gordon Museum, Guy's Hospital, London SE1 9RT, UK
Correspondence to: Mr J. D. Maynard

Cystic changes in the parotid gland are found occasionally in long-standing parotid obstruction. The cysts are multiple and usually <0·5 cm in diameter. Lymphangiomas occur occasionally in children and are obvious at operation. Solitary cysts in otherwise normal glands are rare but are more commonly seen in the parotid than the submandibular salivary gland. They account for 2–5 per cent of all parotid masses or space-occupying lesions[1]. Because cystic degeneration occasionally occurs in salivary neoplasms, all solitary cystic lesions in the parotid were widely excised after nerve dissection. The results of this policy are presented.

Clinical description

Since 1967 a personal series of 324 parotidectomies was carried out for parotid masses. A parotid mass was defined as a probable cyst if it was obviously fluctuant on clinical examination and the diagnosis confirmed if it was clearly a cyst at operation. Twenty-four solitary cysts were widely excised during this period, an incidence of 7·4 per cent. In ten cases the histology showed the cyst to be a neoplasm—a surprisingly high incidence of nearly 42 per cent (*Table 1*). Included among the non-neoplastic cysts were two large solitary cysts measuring 8 and 10 cm arising below the parotid and extending deep to the gland. They were thought on histological examination to be branchial cysts of second branchial cleft origin[2]. Three smaller cysts between 2 and 4 cm diameter lying in the central part of the parotid deep to the facial nerve and lined with squamous stratified epithelium were perhaps of first branchial cleft origin[1,3].

The four cysts, classified as dermoid cysts, had arisen in the lower pole of the parotid and one on the anterior border and ranged between 1 and 2 cm in diameter.

The neoplastic cysts were indistinguishable from the other cysts both clinically and at operation. Those that were pleomorphic adenomas had undergone central cystic degeneration One measured 8 × 6 cm, was deep to the facial nerve and extended deeply behind the oropharynx. It had been explored abroad and left intact. It had the appearance of a thin-walled branchial cyst containing milky fluid It was uncertain on histological examination whether it was a monomorphic or pleomorphic adenoma. One of the adenolymphomas was in the central part of the parotid; it had been repeatedly aspirated elsewhere and cytology had failed to demonstrate the presence of a neoplasm. The squamous cell carcinoma was a 1-cm plaque on the wall of a 4-cm thin-walled cyst. The four pleomorphic adenomas and the two carcinomas were followed up for a maximum of 15 years without recurrence.

There were few complications of the operations. One patient with an infected probable first cleft branchial cyst has permanent weakness of the lower lip. A branch of the lower division of the facial nerve was closely adherent to the cyst wall and partly divided and then sutured. The remaining patients had no late detectable weakness of the facial nerve and there were no other complications of surgery, except five patients with mild Frey's syndrome.

Table 1 *Histology of 24 solitary parotid cysts*

Non-neoplastic cysts	*n*	Neoplastic cysts	*n*
Second cleft branchial cysts	2	Pleomorphic adenomas	4
First cleft branchial cysts	3	Adenolymphoma	4
Dermoid	4	Muco-epidermoid tumour	1
Hamartoma	1	Squamous cell carcinoma	1
Cyst lined with granulation tissue	1		
Cysts lined with cuboidal cells	3		
Total	14	Total	10

Discussion

There is little in the literature about solitary cysts of the parotid. Bell and O'Neill[4] described 1 cystic hygroma and 2 branchial cysts in a series of 77 parotidectomies for tumour (3·9 per cent). Work and Hecht[5] described 2 congenital cysts in a series of 64 parotidectomies for non-neoplastic disease and discussed cysts which had resulted from obstructive disease of the parotid. Such cases have been excluded in this series. Polayes and Rankow[6] discussed tumours of the accessory lobe of the parotid In a series of seven cases there were five neoplasms, one haemangioma and two cysts. The latter were thought to be associated with chronic sialo-adenitis. Pratt[7] discussed cystic lesions of the parotid; the majority of these cases were the result of inflammatory disease, ductal obstruction, calculi, Sjogren's disease and 'Mikulicz' disease. He described epidermoid cysts and included cysts resulting from trauma, more commonly called sialoceles. Neoplastic cysts were not described.

In this series of patients, the cause of traumatic sialoceles was obvious and they have been excluded, as have the cysts associated with obstructive disease, calculi or Sjögren's disease.

It is not the intention of this paper to discuss the aetiology of benign parotid cysts but to draw attention to the high incidence of neoplasms (42 per cent). If the four benign adenolymphomas are excluded, the four pleomorphic adenomas and two carcinomas still produce an incidence of 25 per cent of neoplasms which are liable to recur if treated conservatively and not widely excised.

The probable aetiology, anatomy and clinical behaviour of anomalies of the first and second branchial cleft have been discussed in some detail by Aronsohn *et al.*[2] and, clearly, total excision of these rare cysts is necessary to prevent infection and sinus formation.

It is possible that with the increasing use of ultrasound in the investigation of parotid masses, more cystic lesions will be diagnosed pre-operatively and, with this pre-operative diagnosis, neoplasms with cystic degeneration may be misdiagnosed. Although this is a very small series of patients from which to draw any firm conclusions, it is suggested that aspiration of cysts found in the parotid or conservative treatment may be unwise and that neoplasia may be missed, or spread. Thus, it may be safer to widely excise all solitary cysts in the parotid gland.

References

1. Work WP. Cysts and congenital lesions of the parotid gland. *Otolaryngologic Clinics of North America* 1977; **10**: 339–43.
2. Aronsohn RS, Batsakis JG, Rice DH, Work WP. Anomalies of the first branchial cleft. *Arch Otolaryngol* 1976; **102**: 737–40.
3. Sobieski EJ, Kleinhenz RJ, Metheny JA Branchiogenic cyst within the parotid gland. *Arch Otolaryngol* 1965; **82**: 395–7.
4. Bell DM, O'Neill JJ Parotid tumours *Ulster Medical Journal* 1970; **39** 48–54
5. Work WP, Hecht DW Non neoplastic lesions of the parotid gland. *Ann Otol Rhinol Laryngol* 1968; **77**: 462–7.
6. Polayes IM, Rankow RM. Cysts, masses and tumours of the accessory parotid gland *Plastic and Reconstructive Surgery* 1979, **64**: 17–23.
7. Pratt LW. Cystic lesions of the parotid region *J Maine Med Ass* 1965, **56**: 21–23.

Paper accepted 1 June 1988

0007-1323/88/101043-01$3 00 © 1988 Butterworth & Co (Publishers) Ltd

Correspondence

Treatment of pancreatic fistula

Sir,

We were interested in the case report by Ahrén, Tranberg and Bengmark (*Br J Surg* 1988, **75**: 718) concerning the treatment of pancreatic fistula with somatostatin analogue SMS 201-995. We have recently had a case which followed a similar course.

A 22-year-old girl with gallstone associated pancreatitis had drainage of a large pancreatic abscess on 31 March 1988. Following this she developed a pancreatic fistula through her drain site. The fistula output fluctuated between 50 and 250 ml per day She was treated conservatively until 17 May 1988. During this time an ultrasound had shown a 4 cm pseudocyst in the head of the pancreas. On 17 May 1988 she was commenced on a 48 h infusion of SMS 201-995 (Sandostatin, Sandoz Ltd., Switzerland) at the rate of 250 μg/h. She then had a further 72 h of subcutaneous Sandostatin in a dose of 100 μg three times a day. The fistula became dry by 36 h, remained so for 24 h, recurred for 12 h and then remained dry.

Over the next 2 weeks the patient complained of increasing upper quadrant pain and eventually a tender mass was palpable in the right upper quadrant. Ultrasound showed an 8 cm cyst in the head of the pancreas. This was aspirated percutaneously but recurred within a week She made a complete recovery after operative cystduodenostomy.

Sandostatin may well be a useful adjunct to conservative management of postoperative pancreatic fistulae but one must still be alert to the development of pseudocysts or enlargement of existing cysts following closure of external pancreatic fistula.

G. A. Fielding
O. J. Garden
D. C. Carter

Royal Infirmary
Glasgow G31 2ER
UK

Meleney's synergistic gangrene

Sir,

Professor W. H. Cole, in his letter (*Br J Surg* 1988; **75**: 619) provides a firsthand account of the difficulty F. L. Meleney experienced in accepting the presence of the trophozoites of *Entamoeba histolytica* in histology sections from the case of postoperative progressive gangrene of the abdominal wall due to amoebiasis reported by Cole and Heideman in 1929[1]. In the field of the surgical complications of intestinal amoebiasis, there have been several instances where the reporting histopathologist has overlooked the presence of *E. histolytica* in biopsy material, and a subsequent re-examination of the same slides has revealed the presence of *E. histolytica*.

In 1931 Gunn and Howard[2] commented on the difficulty in the histological diagnosis of amoebiasis, and the need for careful and prolonged search for the amoebae. In one of their cases (a man aged 41) a biopsy from an amoeboma of the caecum had been reported as showing non-specific chronic inflammation but, when the slides were reviewed later, *E. histolytica* was detected.

In 1958, Jumper, Steel and Chester[3] described the case of a man aged 32 who underwent appendicectomy· the histologist reported the excised appendix as showing acute appendicitis: but a year later the patient was diagnosed as having amoebic colitis and the review of the original appendix slides revealed the presence of *E. histolytica*.

More recently in 1984, Robinson and Levinson[4] reported the case of a man aged 54 who was found to have an amoebic liver abscess; but 2 months earlier he had had his appendix removed and the histology report had been acute appendicitis, a review of the appendix sections showed that the trophozoites of *E. histolytica* were present

In the same year Sanderson and Walker-Smith[5] described how, in a boy aged 8, a diagnosis of chronic inflammatory bowel disease had been made after a biopsy of the colon had been reported as non-specific granulomatous inflammation, however, subsequent stool examinations were positive for amoebiasis, and a review of the original biopsy section showed that *E. histolytica* was present

This tendency for the presence of amoebae to be overlooked in routine histological examinations goes some way to explain how the amoebic aetiology of Meleney's synergistic gangrene had remained unrecognized for so long.

Another important factor was the undoubted success of surgery; this had the purely practical effect of making further investigations regarding the aetiology of the gangrene appear unnecessary. Leonard[6] in 1944 summarized the surgeon's point of view with these words. 'Diagnosis may be made from the clinical picture and effective treatment instituted without confusing and controversial bacterial studies.'

Thus the probable amoebic aetiology of Meleney's postoperative progressive gangrene, as proposed by Cole and Heideman in 1929[1], failed to gather significant support by subsequent investigators largely because the specialized studies necessary to demonstrate the presence of *E. histolytica* in material from such cases were not carried out.

L. Turner
J. Davson*
D. M. Jones

University Hospital of Manchester
** University of Manchester*
Manchester
UK

1. Cole WH, Heideman ML Amebic ulcer of the abdominal wall following appendectomy with drainage. *J Am Med Assoc* 1929; **92**: 537–40.
2. Gunn H, Howard NJ Amebic granulomas of the large bowel. Their clinical resemblance to carcinoma. *J Am Med Assoc* 1931; **97**: 166–70.
3. Jumper K, Steele VW, Chester CL. Rectal biopsy in the diagnosis of amebic colitis. *South Med J* 1958; **51**. 545–53.
4. Robinson AS, Levinson M Amebic appendicitis associated with hepatic abscess *South Med J* 1984; **77**: 1047–8.
5. Sanderson IR, Walker-Smith JA. Indigenous amoebiasis: an important differential diagnosis of chronic inflammatory bowel disease. *Br Med J* 1984; **289**: 823.
6. Leonard DW. Progressive gangrene in an abdominal wound *Arch Surg* 1944, **48**: 457–64.

Single-duct discharge from the nipple

Sir,

The paper by Mr Locker *et al.* (*Br J Surg* 1988; **75**: 700–1) has the admirable aim of reducing unnecessary microdochectomies. Unfortunately the study divides the cases only into those with overtly blood-stained discharges and those with non-blood-stained discharges. Locker briefly alluded to the paper from Guy's which found that all cases of single-duct discharge were positive on testing the discharge for haemoglobin. We would certainly agree that many haemoglobin negative discharges can be treated expectantly. Nevertheless, this simple test should be routinely applied to the testing of single-duct discharges When haemoglobin is detectable, in our opinion a microdochectomy is indicated because it is not only a diagnostic, but also a therapeutic procedure, and when used selectively can provide effective treatment for troublesome nipple discharges. In addition, when used in this way cases of malignancy will not be missed

M. A. Chaudary
I. S. Fentiman

Guy's Hospital
London SE1 9RT
UK

True aneurysms of the pancreaticoduodenal artery

Sir,

While we would agree with Small *et al.* (*Br J Surg* 1988; **75**: 721) that the diagnosis of aneurysm of the pancreaticoduodenal artery has in the past presented difficulties to the clinician, mention should be made of the ease by which this diagnosis can be made in both the symptomatic and asymptomatic patient by the use of ultrasound. Within the last 12 months we have diagnosed two such aneurysms at this institution. one totally asymptomatic and unexpected and one suspected but also asymptomatic. Caution is necessary however since these aneurysms often appear non-pulsatile on real-time scanning and may be mistaken for cysts[1]. In our experience we have also noticed the absence of visible pulsation and rely on the use of pulsed Doppler to confirm the diagnosis.

P. Grech
P. C. Rowlands

St. Mary's Hospital
London W2 1NY
UK

1. Ugolotti U, Miselli A, Mandrioli R, Larini P, Ross A. Ultrasound diagnosis of superior mesenteric artery aneurysm: two case reports. *J Clin Ultrasound* 1984; **12**· 581–4.

Mortality after surgery for chronic pancreatitis

Sir,

We were very interested in the recent report by A. Mannell and colleagues (*Br J Surg* 1988; **75**. 467–72), indicating the long-term mortality rate of 141 patients operated on with chronic pancreatitis. The main indication (95 per cent) for surgery was intractable pain. The authors compared the expected *versus* observed long-term survival and concluded the difference was highly significant. This could lead to the conclusion that elective surgery is responsible not only for postoperative mortality but also for long-term mortality. In our opinion, this comparison is open to criticism because patients operated on should be compared with patients not operated on but submitted to the same risk factors, mainly alcoholism and tabagism and their multivisceral repercussions (i.e. alcoholic hepatopathy, cancer, etc.).

We studied 275 patients (238 men; 246 alcoholics) with chronic pancreatitis and compared the long-term mortality rate between patients undergoing elective pancreatic surgery or not. In all, 141 patients underwent elective pancreatic surgery Types of elective pancreatic surgery were: Whipple operation ($n=27$); distal pancreatectomy ($n=52$); cystic, pancreatic, biliary or digestive drainage ($n=85$). Indications for surgery included not only intractable pain but also chronic and acute complications of chronic pancreatitis. The control group consisted of patients not operated on ($n=92$) or patients operated on for non-elective surgery ($n=19$). There was no difference between the two groups for sex, alcoholism and age at onset of chronic pancreatitis. The length of follow-up was longer for patients operated on than for the control group (9·4±6·7 *versus* 7·5±5·2 years). There were 62 deaths: 18 in the control group; 44 in the operated group including 7 postoperative deaths. Mortality rate for patients submitted to elective pancreatic surgery (26 8 per cent) was significantly higher than for the control group (16·2 per cent) ($P<0·03$). This difference was explicated by the postoperative mortality. In contrast, cumulative survival rates (compared by log rank test) were not statistically different for the elective pancreatic surgery group or the control group after 15 years of evolution of chronic pancreatitis. We conclude that elective pancreatic surgery is responsible for 7 of 62 deaths of patients with chronic pancreatitis (11·3 per cent) but had no influence on long-term mortality.

P. Levy
P. Bernades
J. Belghitti
F. Fekete

Hopital Beaujon
92118 Clichy cedex
France

Author's reply

Sir,

I note with interest the experience reported by Levy *et al.* However, I would draw their attention to two points:

1. Long-term survival after surgery for chronic pancreatitis was not compared with patients managed medically, but to the normal population.
2 Elective pancreatic surgery in this Mayo Clinic series was responsible for 1/141 deaths of patients with chronic pancreatitis, a mortality rate of less than 1 per cent.

A. Mannell

University of the Witwatersrand
Johannesburg
South Africa

Endoscopic sclerotherapy for oesophageal varices in children

Sir,

The article by Howard *et al.* on endoscopic sclerotherapy for the management of oesophageal varices in children (*Br J Surg* 1988; **75**· 404–8) omits discussion of an important treatment option, namely selective variceal decompression. Their results with sclerotherapy are indeed excellent at mean follow-up of 3·6 years. We agree 100 per cent with the policy of initial sclerotherapy for all children with intrahepatic disease as in many of these the ultimate therapy will be liver transplantation. However, we would raise the question of whether sclerotherapy is the only, or even the correct, treatment option for patients with extrahepatic portal vein thrombosis (PVT) as the aetiology of their variceal bleeding.

Selective variceal decompression should be considered in treatment options for such patients. The need for definitive control of bleeding in this population with normal liver function and an otherwise normal life expectancy makes them ideal candidates for a 'curative' surgical procedure. In a recent review of our experience[1] with 70 patients bleeding from varices secondary to PVT, we have found the following:

1. Distal splenorenal shunt could be performed in 80 per cent of patients who had had no prior surgical therapy, with a 96 per cent patency rate.
2. Continued portal perfusion, quantitative hepatic function, and liver volume were maintained in distal splenorenal shunt patients
3. Other surgical procedures (splenectomy, central splenorenal shunt, makeshift shunts, and devascularization procedures) had a high failure rate.
4. Sclerotherapy, performed when distal splenorenal shunt was not an option, had a rebleeding rate of 28 per cent at a mean follow-up of 50 months.

While the surgical literature is not large on the use of distal splenorenal shunt for patients with PVT, several centres have reported on its use[1–5]. The advantages of this procedure over other management methods are:

a) Good portal flow, and hence prevention of development of the portaprival syndrome[6], is maintained through hepatopetal collaterals.
b) Good shunt patency is maintained because it is a high flow 'end' shunt from a large spleen, rather than a low flow side-to-side shunt
c) The spleen is retained, which is advantageous in children, but its volume is significantly reduced and hypersplenism improved[1].
d) Patients do not have to return for multiple procedures (scleropathy), particularly when advocated to be done under anaesthesia as in the cited paper

The authors of the current paper do discuss the complications of sclerotherapy, but we would add one further caution. The haemodynamics of patients with portal hypertension secondary to extrahepatic portal vein thrombosis differ from patients with cirrhosis. The normal intrahepatic sinusoidal pressure in the former group encourages collateral flow from the obstructed portal venous bed to the liver. This we believe, but have not proved, may result in increased retrograde passage of sclerosant into intra-abdominal veins at the time of sclerotherapy with subsequent thrombosis. To achieve the desired thrombosis of the gastro-oesophageal varices, without thrombosis of the splenic vein which is open at initial study in the majority of these patients[1], may be difficult to achieve. Splenic vein thrombosis precludes the chance of a curative distal splenorenal shunt. Before widespread application of sclerotherapy in this population, the onus should be put on its proponents to document that detrimental extension of intra-abdominal venous thrombosis does not occur. This requires careful arteriographic study, such as has been used to document the course after distal splenorenal shunt[1].

At the present time, longer follow-up, particularly with a life expectancy of more than 50 years in this population, is needed both in our own series and in the currently reported series. This must determine the long-term control of bleeding, shunt patency, and occurrence of other morbidity. We believe it is important, in the interests of optimal patient management, to point out that the definitive answer is not yet available for the subset of patients with PVT, and that there is, in the 1980s, a realistic definitive surgical alternative.

W. D. Warren
J. M. Henderson

Emory University School of Medicine
Atlanta
USA

1. Warren WD, Henderson JM, Millikan WJ *et al.* Management of variceal bleeding in patients with non-cirrhotic portal vein thrombosis. *Ann Surg* 1988; **207**. 623–34.
2. Fonkalsrud EW. Long-term results following surgical management of portal hypertension in children. *Z Kinderchir* 1982; **35** 57–61.
3. Maksoud JG, Mies S. Distal splenorenal shunt in children *Ann Surg* 1982; **195**: 401–5.
4. Bhalerao RA, Pinto AC, Bapat RD *et al.* Selective transplenic decompression of oesophageal varices by distal splenorenal shunt and splenocaval shunt *Gut* 1978; **19** 831–7.
5. Rodgers BM, Talbert JL. Distal splenorenal shunt for portal decompression in childhood. *J Ped Surg* 1979; **14**: 33–7
6. Warren WD, Millikan WJ, Smith RB *et al* Non-cirrhotic portal vein thrombosis. Physiology before and after surgery. *Ann Surg* 1980, **192**: 341–50.

Incidence of deep vein thrombosis after major abdominal surgery in Brisbane

Sir,
We felt that the report of Reasbeck *et al.* (*Br J Surg* 1988; 75: 440) raised a few interesting points. Although it is not explicitly stated, the impression created by the authors is that this was a prospective trial. Their methodology, however, raises serious doubts about the validity of the findings. First, despite the exclusion criteria that were apparently adhered to, 15 patients entered the trial who were administered perioperative anticoagulants, and 2 patients were entered who had a previous history of leg vein thrombosis. Secondly, it is well recognized that ^{125}I fibrinogen scanning in patients with oedema and leg ulcers is of limited value Why then were at least five patients with these conditions submitted to scanning? Thirdly, to administer potassium iodide for 1 month is far in excess of the usual time that is required to suppress thyroid uptake of ^{125}I fibrinogen.

Our greatest reservations with this study, however, are in regard to the results. Of the 44 patients who were submitted to both venography and scanning, there was agreement between these investigative modalities in only 27 (61 per cent) of patients. If one accepts the concensus of experience that venography is 'the gold standard' then this raises the question whether the ^{125}I fibrinogen technique used by this group does not suffer from serious problems—particularly as most studies have found a correlation of about 90 per cent in the detection of distal leg vein thrombosis[1,2]

In addition, it was interesting to read that 27 per cent of patients who had low-dose subcutaneous heparin, perioperatively, suffered a postoperative deep vein thrombosis (confirmed by both scanning and venography). This compares rather unfavourably with the overall incidence of deep vein thrombosis of 24 per cent and negates the final conclusion that deep vein thrombosis prophylaxis should be encouraged in Brisbane.

The only valid conclusion that can be drawn from this study is that there was no correlation between ^{125}I fibrinogen scanning and venography in the detection of deep vein thrombosis

J. O. Chleboun
M. M. D. Lawrence-Brown
S. Baker

Repatriation General Hospital
Perth
Australia

1. Browse NL The ^{125}I fibrinogen uptake test. *Arch Surg* 1972; **104**· 160.
2. Kakkar V. The diagnosis of deep vein thrombosis using the ^{125}I fibrinogen test. *Arch Surg* 1972; **104**: 152

Author's reply

Sir,
I am grateful for the opportunity to respond to the points raised by Chleboun *et al.* in response to the above report. The trial was indeed a prospective trial. Although patients receiving perioperative subcutaneous heparin were indeed excluded according to the protocol, a number of these patients were nevertheless given heparin without our prior knowledge by the consultant surgeons concerned. Of these, the vast majority in fact received heparin only postoperatively (a practice which we feel is of questionable value but from which we have been unable to dissuade some of our colleagues to desist). In fact only one patient, not two, was entered who had had a previous deep vein thrombosis and as pointed out in our paper this was a diagnosis made retrospectively on a postoperative venogram and there was no pre-operative clinical history of thrombosis Three patients developed bilateral oedema of the legs postoperatively but this was not present pre-operatively and was therefore not a ground for exclusion. The leg ulcers in the other two patients were small and may in fact not have interfered with the results of the scans but, as pointed out in the paper, we were at pains to avoid over-diagnosing deep vein thrombosis and therefore assumed that the scans in these patients were in fact false positives.

I take the point that there was considerable discrepancy between the results of ^{125}I fibrinogen scans and venography and I believe this is one of the most important messages of the paper. As we pointed out, criteria for interpretation of fibrinogen scans in previous studies have been rather variable and we believe that fibrinogen scanning may be an unreliable screening modality for postoperative venous thrombosis unless supplemented by other tests. All fibrinogen scans were carried out by the same doctor taking great care to adhere precisely to criteria laid down by early workers in the field[1–3]. Early in the study, when the discrepancy between the results of scans and venograms became apparent, we were at great pains to exclude, subsequently, any technical deficiencies in the performance of scans which could have caused this discrepancy No change in the discrepancy between scans and venograms occurred as a result

As I have already pointed out, most of the patients who had low dose subcutaneous heparin received this only postoperatively, and therefore it is not surprising in my view that this treatment resulted in an incidence of deep vein thrombosis which was not significantly different from that observed in patients who received no heparin prophylaxis. I do not believe this observation negates the conclusion that deep vein thrombosis prophylaxis should be encouraged in Brisbane; if the incidence of postoperative deep vein thrombosis here is the same as in other areas where prophylaxis is considered appropriate and necessary it would seem logical to suggest that prophylaxis should also be practised here.

The conclusion that there was no correlation between ^{125}I fibrinogen scanning and venography in the detection of deep vein thrombosis is indeed valid. In the context of many previous studies of the effectiveness of prophylactic techniques which have relied solely on fibrinogen scanning to detect postoperative deep vein thrombosis I believe this conclusion is an extremely important one.

P. G. Reasbeck

Princess Alexandra Hospital
Woolloongabba
Australia

1 Flanc C, Kakkar VV, Clarke MB. Postoperative deep vein thrombosis—effect of intensive prophylaxis. *Lancet* 1969; i: 477–9.
2. Kakkar VV, Nicolaides AN, Renney JGT, Friend JR, Clarke MB. ^{125}I-labelled fibrinogen test adopted for routine screening for deep vein thrombosis. *Lancet* 1970; i: 540–2.
3. Kakkar VV. The diagnosis of deep vein thrombosis using the ^{125}I fibrinogen test. *Arch Surg* 1972; **104**: 152–9

Sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts

Sir,
We thank Mr Pickard *et al.* for their comments (*Br J Surg* 1988; **75**. 291) on our paper[1]. We are aware that if the mean arterial blood pressure in a previously normotensive patient falls below 50–60 mmHg, cerebral ischaemia may result and this threshold will probably be higher in patients who were hypertensive pre-operatively This is why we were careful to maintain the mean arterial pressure in our patients to above 70 mmHg. None of our patients with extrahepatic obstruction or non-cirrhotic portal fibrosis had systemic arterial hypertension.

We have not compared the pre- and postoperative neuropsychological assessment of our patients who had sodium nitroprusside but will now do so. In non-cirrhotic portal fibrosis the results will be difficult to interpret as we have found subclinical changes in 40 per cent after shunts[2]. However, in patients with extrahepatic obstruction where portosystemic encephalopathy does not occur[3], this assessment may be very useful. We thank your correspondents for these suggestions.

T. S. Jayalakshmi
S. Nundy

All India Institute of Medical Sciences
New Delhi-110029
India

1. Sood S, Jayalaxmi TS, Vijayaraghavan S, Nundy S. Use of sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension. *Br J Surg* 1987; **74**. 1036–8
2. Sarin SK, Nundy S. Subclinical encephalopathy after portosystemic shunts in patients with non-cirrhotic portal fibrosis *Liver* 1985; **5**: 142–6
3 Pande GK, Reddy VM, Kar P *et al.* Operations for portal hypertension due to extrahepatic obstruction: results and 10 year follow up. *Br Med J* 1987; **295**· 1115–7.

Book reviews

Surgical Infectious Diseases

R. J. Howard and R. L. Simmons. 218 × 285 mm Pp. 913 Illustrated. 1988. Englewood Cliffs, New Jersey. Prentice Hall $141 50

This book extends to 913 pages with contributions from 71 North American authors and represents an authoritative source of information for all surgeons irrespective of their specialty. The book is subdivided into eight parts comprising several chapters each and is well illustrated with good quality line diagrams and photographs. The text is extensively referenced, some 4327 in all!

Part 1 deals with the microbiology of organisms encountered in surgical practice whilst parts 2 and 3 move on to describe host defence mechanisms, the inflammatory response and local and systemic responses to infection There is some repetition in these chapters which is inevitable in such a multi-author volume

A resumé of laboratory diagnosis is then considered in part 4. The book continues with a section on antimicrobial agents and immunotherapeutic approaches to surgical sepsis. Part 6 concerns itself with wound infections in general and contains an excellent chapter on technical factors which may help to prevent wound sepsis. However, not all UK surgeons would agree with the statement that tetracycline lavage of the peritoneal cavity should not be recommended, or with the opinion that anti-anaerobic agents are of limited value in the treatment of intraperitoneal sepsis In the penultimate section, regional surgical infections are concisely described but the omission of *Campylobacter pylori* and its role in the pathogenesis of gastritis make this section less than complete The book rounds off by considering special problems in surgical infection which includes an excellent and timely discussion of the problems posed by HIV infection

I would thoroughly recommend this majestic volume which will make a worthy addition to any library shelf.

N. Carr

Senior Registrar in Surgery
The Middlesex Hospital
London W1N
UK

1987 Year Book of Surgery

S I Schwartz 156 × 235 mm. Pp 452. Illustrated. 1987 London· Wolfe Medical Publications. £40 00

This book represents a genuine attempt to cover a wide spectrum of surgical topics by surveying an extensive range of journals The contents include synopses of papers covering all the major specialities and in addition useful chapters concerning the management of shock, trauma, wound healing, infection, burns and oncology and immunology. The main structure of the book is a series of synopses on papers published a year before followed by a discussion by one of the editors. On the whole I found the discussions to be well written and informative My one slight criticism of this book is that I think it attempts to cover too many specialities and therefore must be limited by the number of topics that it can possibly cover within one speciality.

S. J. Snooks

Senior Registrar in Surgery
St Bartholomew's Hospital
London EC1A 7BE
UK

Surgical Care for the Elderly

R Benton Adkins 178 × 258 mm. Pp. 542. Illustrated. 1988 Williams and Wilkins £58 00.

In no way does this American book endeavour to convince its readers that there should be a separate surgical service for the elderly as has developed in geriatric medicine. The editor's definition of elderly is of 65 years or more and the overall theme is that more credit should be given to functional than chronological age

This volume has 37 chapters and covers a wide range of aspects of surgical care in the elderly in the USA. Subject matter ranges from nursing and health information management, and passes through each organ system and surgical discipline to wind up with neuro-psychiatric problems and prediction of future trends. Twenty-eight of the 37 chapters focus on particular specialist care areas and some of these face up to the geriatric variations more specifically than others Although the potential spectrum of discussion is large, omissions do occur There was, for example, little coverage of prostatectomy and stoma care in the elderly. Also, although difficult to commit to paper, a chapter highlighting surgical technique, and pitfalls in the high risk emergency elderly patients, especially for the benefit of surgeons in training, would have been relevant. All authors promote an optimistic overview of surgical procedures in the elderly, particularly with elective surgery. The fact that results of emergency surgery in the elderly are less often favourable is frequently referred to but the problem of how to entice such patients from the community for elective procedures is not broached

As with all multi-author textbooks some repetition is inevitable but this book is a useful reference text and serves to remind all surgeons and those engaged in surgical care of the elderly of the increasing burden of responsibilities in these brittle patients

M. K. H. Crumplin

Consultant Surgeon
Wrexham
UK

Atlas of Stapling Techniques

F. A. Rubio. 231 × 310 mm. Pp. 329 Illustrated. 1986 Rockville, Maryland, USA: Aspen Publishers Inc

This is a comprehensive manual of surgical stapling. The initial chapters describe the various types of stapling instruments available, with precautions for their use There are then sections on the use of staples in general surgery, pulmonary surgery, urology, cardiovascular surgery and gynaecology The various procedures are described in brief notes explaining each step with, on the facing page, excellent line diagrams demonstrating these stages. At the end of the book is a comprehensive list of references for more detailed information on the techniques described

However, the author does tend to go from the sublime to the ridiculous; from describing complex procedures, e.g oesophageal replacement using reversed gastric tubes requiring multiple firings of different stapling instruments, to using an LDS powered stapler for such operations as vasectomies and cholecystectomies, which is clearly economically unjustifiable at over £60 per procedure

Inevitably, in an area where technology is advancing rapidly, such a book is soon going to become out-dated In fact, this has already occurred. since publication a new range of circular stapling devices, which modify the techniques used in the important areas of anterior resection and oesophageal anastomoses, has been introduced But, overall, this book is a useful reference manual for those surgeons contemplating the use of staples, and also for the committed stapler

C. Royston

Consultant General Surgeon
Hull
UK

Erratum

'Clinicopathological assessment and staging of colorectal cancer', by N. S. Williams, J. R. Jass and J. D. Hardcastle, *Br J Surg* 1988, **75** 649–652, page 651, right hand column, lines 17–18: for '*Non-curative owing to the presence of residual local disease.* This *may* be confirmed by histological examination.' read '*Non-curative owing to the presence of residual local disease* This *must* be confirmed by histological examination.'. We apologize for this error.

Notices and announcements

20 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

24–27 October 1988
American College of Surgeons Meeting: 74th Clinical Congress
Chicago, USA
Information Fred C Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

26 October 1988
British Society for Surgery of the Hand. Basic course: Care of Hand Injuries. Advanced course: Reconstructive Surgery after Trauma
London, UK
Information: Honorary Secretary of BSSH at the Royal College of Surgeons, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

30 October–1 November 1988
13th Congress of the European Society for Medical Oncology (ESMO)
Lugano, Switzerland
Information: Dr F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

30 October–5 November 1988
Expanding Horizons of Diagnostic Ultrasound
Bath, UK
Information Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

4–7 November 1988
Integrated Management of Head and Neck Cancer
Grantham, UK
Information Mr P. J. Bradley, Consultant ENT Surgeon/Head and Neck Oncologist, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK

17–19 November 1988
Eighth Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information: Mrs Marty May, Secretary to LTC Warren. F Bowland MD, Chief, Trauma Service, Department of Surgery, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

24–25 November 1988
Annual Meeting of the Vascular Surgery Society of Great Britain and Ireland
Leeds, UK
Information: Mrs P. D. Huxtable, Flipper Pharmaceuticals Ltd., Harrier House, High Street, West Drayton, Middlesex UB7 7QG, UK

25–27 November 1988
22nd Annual Combined Surgical Meeting
Singapore
Information: The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

28 November–2 December, 1988
Symposium and Workshop on Vascular Surgery
Singapore
Information The Secretariat, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0306

8th December 1988
British Association of Surgical Oncology Forum: 'Head and Neck Cancer for the General Surgeon'
London, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

9 December 1988
Angioplasty: a Surgical or Radiological Procedure
London, UK
Information Janet Williamson, Secretary to Frank Ellis, 5 New Guy's House, Guy's Tower, London SE1 9RT, UK

9–10 December 1988
British Association of Surgical Oncology Forum: Winter Meeting
London, UK
Information: British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–18 December 1988
Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons
Las Vegas, USA
Information: Dr M. R. Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988
Association of Surgeons of India Golden Jubilee Annual Conference
New Delhi, India
Information Dr N C. Madan, Organizing Secretary 'ASICON-88', Room No. 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

21–22 January 1989
Hong Kong Surgical Forum
University of Hong Kong, Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

12–18 February 1989
Diabetic Control and Complications: An Interactive Workshop
London, UK
Information: Director, Courses Department, 65 Davies Street, London W1Y 2AA

17–19 February 1989
The Fifth Biennial Conference of the Indian Association of Chemotherapists
Bombay, India
Information: Dr Nagraj G. Huilgol MD, Organizing Secretary, Nanavati Hospital and Medical Research Centre, S.V. Road, Vile Parle (West), Bombay 400056, India

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information. Congress Secretariat, 7th Congress Ssian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

12–15 March 1989
Current Problems in Breast Cancer
Vienna, Austria
Information: Secretariat ICS, Elisabeth Ribar-Maurer, c/o Wiener Medizinische Akademie, Alser Strasse 4, A 1090 Vienna, Austria

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information. The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

12–14 April 1989
VIth International Conference: Polymers in Medicine and Surgery
Leeuwenhorst Congress Centre, The Netherlands
Information. Joanna Evans-Thomas, Conference Officer, The Plastics and Rubber Institute, 11 Hobart Place, London SW1W 0HL, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information. The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

Contents

The American Journal of Surgery

SEPTEMBER 1988/VOLUME 156/NUMBER
(PART 1 OF 2)

EDITORIAL OPINION

153 **The National Cancer Institute's Clinical Alert on Breast Cancer: Why the Hurry?**
John S. Spratt

ASSOCIATION FOR SURGICAL EDUCATION

155 **The Surgical Clerkship Experience: Self, Departmental, and Institutional Assessment**
Jocelyn D. Ten Haken, Judith G. Calhoun, Kenneth A. Frank, Linda C. Youmans, and Gerald B. Zelenock

SCIENTIFIC PAPERS

159 **Importance of Cause in the Outcome of Pancreatic Pseudocysts**
Clement W. Imrie, Laura J. Buist, and Michael G. Shearer

163 **Surgical Management of the Acutely Obstructed Colon. A Review of 127 Cases**
Kenman J. Buechter, Charles Boustany, Raymond Caillouette, and Isidore Cohn, Jr.

169 **Distal Splenorenal Shunt: Standard Procedure for Elective and Emergency Treatment of Bleeding Esophageal Varices**
Robert L. Mitchell and Joseph A. Ignatius

173 **Radical Neck Dissection: Is It Enough?**
William B. Farrar, William R. Finkelmeier, Daniel P. McCabe, Donn C. Young, Patrick J. O'Dwyer, and Arthur G. James
176 **Editorial Comment**
Alfred S. Ketcham

177 **Surgical Treatment of Graves' Disease**
Jean Philippe Ozoux, Loik de Calan, Gerard Portier, Bernard Rivallain, Jean Paul Favre, Alain Robier, Dominique Goga, and Jacques Brizon
181 **Editorial Comment**
Thomas S. Reeve

182 **Who's Afraid Of The Dentate Line? The Whitehead Hemorrhoidectomy**
Julius C. Bonello

187 **Craniofacial Resection for Tumors of the Nasal Cavity and Paranasal Sinuses**
Valerie J. Lund and Donald F.N. Harrison

191 **Cyclosporin A and Islet Function**
Giacomo Basadonna, Francesco Montorsi, Kenji Kakizaki, and Ronald C. Merrell

194 **Canine Motility and Gastric Emptying After Subtotal Gastrectomy**
Sabine Bühner, Hans Jörg Ehrlein, Gert Thoma, and Volker Schumpelick
200 **Editorial Comment**
Michael P. Hocking

201 **Surgical Disorders of the Pancreas in Infancy and Childhood**
Alan Y. Synn, Sean J. Mulvihill, and Eric W. Fonkalsrud

206 **Is Percutaneous Nephrostomy for Hydronephrosis Appropriate in Patients With Advanced Cancer?**
Richard D. Keidan, Richard E. Greenberg, John P. Hoffman, and James L. Weese

209 **A Four-Technique Comparative Study of Orthotopic Liver Transplantation in the Rat**
Antonio Marni and Maria Elena Ferrero

HOW I DO IT

214 **Tube Decompression of the Dilated Colon**
Robert E.H. Khoo, David A. Rothenberger, W. Douglas Wong, John G. Buls, and John S. Najarian

REVIEW

217 **Receptors**
Mark Lane Welton and Edward Passaro, Jr.

224 **Book Reviews**

227 **Letters to the Editor**

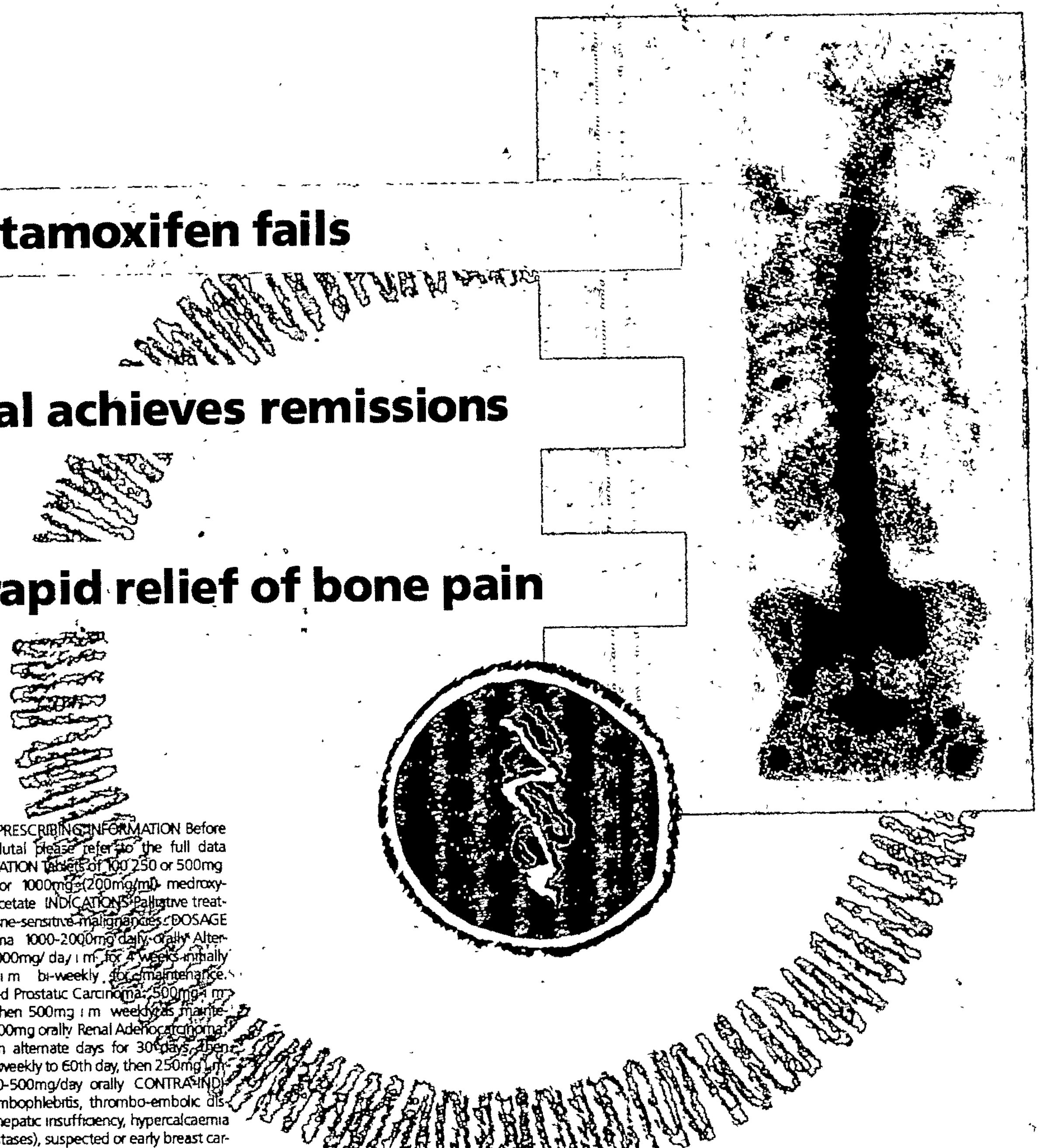
A20 *The British Journal of Surgery* **Table of Contents (vol. 75, no. 9, September 1988)**

Part 2, 1B **Advances in Surgical Technologies: Guide to Medical Equipment and Supplies**

When tamoxifen fails

Farlutal achieves remissions

With rapid relief of bone pain



ABBREVIATED PRESCRIBING INFORMATION Before prescribing Farlutal please refer to the full data sheet PRESENTATION Tablets of 100 250 or 500mg Vials of 500 or 1000mg (200mg/ml) medroxyprogesterone acetate INDICATIONS Palliative treatment of hormone-sensitive malignancies DOSAGE Breast Carcinoma 1000-2000mg daily orally Alternatively, 500-1000mg/ day i m for 4 weeks initially and 500mg i m bi-weekly for maintenance. Endometrial and Prostatic Carcinoma: 500mg i m twice weekly then 500mg i m weekly as maintenance or 100-500mg orally Renal Adenocarcinoma: 500mg i m on alternate days for 30 days, then 500mg i m bi-weekly to 60th day, then 250mg i m weekly, or 100-500mg/day orally CONTRA-INDICATIONS Thrombophlebitis, thrombo-embolic disorders, severe hepatic insufficiency, hypercalcaemia (osseous metastases), suspected or early breast carcinoma, missed abortion, metrorrhagia, pregnancy Hyper-sensitivity to hydroxybenzoates (i m formulation only) WARNINGS AND PRECAUTIONS Discontinue treatment after thrombo-embolic episodes, migraine or ocular problems Care in diabetes or hypertensives Rarely congenital cardiac malformation in the neonate, and masculinisation of female foetuses can occur after use in pregnancy Malignant mammary nodules have occasionally been seen in beagle dogs although their relevance to humans is not known SIDE EFFECTS After i m injection local lesions can occur which may be minimised by injecting deeply into healthy gluteal muscle Progestogenic and adrenergic-like tremor reactions have been reported Corticoid-like effects may also occur Cholestatic jaundice has occasionally been reported LEGAL CATEGORY POM PACKAGE QUANTITIES, BASIC NHS PRICE AND PRODUCT LICENCE NUMBERS 100 x 100mg tablets – blister strips £34 00 3433/0056 50 x 250mg tablets – blister strips £40.00 3433/0058 56 x 500mg tablets – blister strips (calendar pack) £8775 3433/0080 500mg vial for injection £12 00 3433/0045 1000mg vial for injection £20 00 3433/0045 FURTHER INFORMATION AND DATA SHEETS ARE AVAILABLE ON REQUEST FROM Farmitalia Carlo Erba Ltd, Italia House, 23 Grosvenor Road, St Albans, Herts AL1 3AW

Farlutal 500 b.d

medroxyprogesterone acetate

A second chance for patients with advanced breast canc